THE CARTWRIGHT LECTURES.

ON THE

GENERAL PATHOLOGY OF FEVER.

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LECTURE I.

THE NATURE OF FEVER.

THERE is no subject in medicine of more general and varied interest than fever. The practitioner in every department of medicine, the pathologist and the physiologist are equally interested in the investigation of the nature and effects of fever. Even the physicist and the chemist, who are not directly concerned with medical science, have lent their aid to the study of animal heat and its disorders. The history of opinion regarding fever is in great part the history of medicine itself, for no feature of the great systems of medicine from Hippocrates and Galen to the present century so characterizes these systems as the views held concerning the nature of fever. In consequence of the importance of the subject and of the number and ability of those engaged in its investigation, it might be supposed that no chapter in medical science would be better understood than that pertaining to fever. That such is not the case is due to the fact which is becoming more and more evident that the reaction of the animal system which we call fever is dependent upon the most fundamental and essential properties of protoplasm and of nerve energy. In proportion as our knowledge of these properties increases and becomes more accurate, we gain a clearer insight into the

complicated processes involved in the production of fever.

I should hardly have selected for this course of lectures a subject where so many problems remain unsolved and which must necessarily be presented in so fragmentary a form, were it not that in all ages the opinions held concerning the nature of fever have controlled measures employed in its treatment. In proof of this, one need not go back to the time when fever was regarded as an almost conscious struggle of an anima with a noxious principle, in which struggle the physician was to interfere as little as possible, or to the time when fever was supposed to result from morbid humors which the physician should aim to eliminate by the production of a critical discharge, or to the period when the treatment hinged upon the belief either in the sthenic or the asthenic nature of fever. In our own time the treatment of fever is intimately connected with the answers variously given to such questions as whether fever aids in the elimination or destruction of infectious agents concerned in its production; whether increased waste of tissue is a constant condition and a source of danger in fever; what part is played by infection and what part by elevation of temperature in causing the grave symptoms of fever; what in addition to lowering of temperature are the effects of so-called antipyretic measures of treatment?

I need hardly say that the subject of these lectures relates to fever as a condition common to all febrile diseases. Some writers understand by the term fever used in this sense merely abnormal elevation of temperature, others elevation of temperature and the symptoms directly caused by this, and still others a complex of symptoms of which increased temperature is the most prominent but not necessarily the cause of the others. In considering the general pathology of fever it is convenient to adopt the last meaning, although it would

doubtless be less confusing if the word fever were applied only to abnormal elevation of temperature.

Increased temperature being the dominant and essential symptom of fever, all discussions as to the nature of fever centre around the question, How is the febrile rise of temperature produced? It is to the consideration of this question that I first invite your attention. As there are other aspects of fever which I wish to discuss, it will be necessary to present the matter belonging to this division of the subject in as succinct a form as is compatible with clearness. Twelve years ago Burdon-Sanderson[1] brought together in an admirable critical review the results of investigations upon this subject up to that period. Since that time important additions have been made to our knowledge of the mode of production of fever.

In the wonderful preservation of a nearly constant temperature which characterizes in health the warm-blooded animals three factors are concerned, viz., the production of heat within the body, the loss of heat from the body, and the regulating mechanism by which the varying heat production and heat loss are so balanced that the internal temperature remains practically constant. It is theoretically possible that the rise of temperature in fever may be due to the disturbance of any one or more of these factors. It becomes necessary, therefore, to consider the behavior of heat production, of heat loss, and of the regulating mechanism in fever.

We will begin with the consideration of the production of heat in fever. The amount of heat produced by the body is estimated by two methods, one known as direct calorimetry, the other as indirect calorimetry. In the method of direct calorimetry the animal is placed in a closed ventilated box surrounded on all sides by a compartment containing water or air, and the amount of heat discharged from the body is determined by the

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[1] Burdon-Sanderson: The Practitioner, 1876.

quantity of heat imparted to the surrounding water or air. If the temperature of the animal remain unchanged during the period of observation, the heat production is equal to the heat loss; if the temperature rise or fall, the amount of heat corresponding to this change of temperature—an amount determined by multiplying the weight of the animal by its specific heat and by the number of degrees of altered temperature—is added to or subtracted from the quantity of heat imparted to the calorimeter. Time will not permit me to enter into experimental details in this connection; it must suffice to say that the method of direct calorimetry necessitates the introduction of a number of corrections which cannot be determined with absolute accuracy, so that the results obtained are of relative rather than of absolute value.

Hitherto the estimation of heat production in fever by determining the entire amount of heat liberated from the body has been made only upon animals in which fever has been artificially produced. The most elaborate researches of this nature are those of Senator[1] and of Wood.[2] The experiments of Wood are of the greater value because he extended his observations over longer periods of time.

In four of the seven calorimetrical experiments of Wood on different fevered dogs comparison can be made of the amount of heat produced hourly in fever with that produced by the same animal when fed and when in a state of hunger. During the period of fever the animal was also in a condition of hunger. I have computed from Wood's tables that the average hourly heat production during seven days described as first and second fever days, is a little over 23 per cent. greater

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[1] Senator: Untersuchungen über d. Fieberhaften Process, Berlin, 1873.

[2] Wood: Fever, A Study in Morbid and Normal Physiology, Philadelphia, 1880.

than that of the healthy animal during a state of hunger, the minimum excess being 1 per cent. and the maximum 55.5 per cent.[1] If a comparison be made of different periods during the existence of fever there are found to be even greater fluctuations in the amount of heat production than these figures would indicate, this amount being sometimes more than double that in hunger and sometimes considerably less than the average production in hunger. Moreover, these experiments show no definite relation between the height of the temperature and the amount of heat produced, nor is it possible to deduce from them any relation between heat production and the different stages of fever, such as the more recent calorimetrical experiments of Wood, Reichert, and Hare[2] appear to show and which will be described later. An important outcome of these as well as of all similar calorimetrical experiments is that, although the heat production of an animal in fever is greater than that under like conditions of nourishment, it is, as a rule, less than that of the same animal upon a full diet.

There are many reasons which make it important to control the experimental results obtained from animals in fever by corresponding observations of human beings. The agents used in producing experimental fever have been generally putrid fluids or pus, the injection of which causes sometimes diminution instead of elevation of temperature. When fever is thus produced, it is usually of short duration and of only moderate intensity, the rise of temperature being rarely more than four degrees, and sometimes not more than one degree Fahrenheit. Moreover, a large part of the important role played

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[1] In making this computation I have corrected some numerical errors in Wood's tables; these errors are not serious and do not affect his conclusions.

[2] Wood, Reichert, and Hare: Therapeutic Gazette, 1886.

by the skin in the regulation of the bodily temperature in man is assumed by the lungs in these animals.

Complete calorimetrical observations of human beings in fever encounter difficulties which have not yet been overcome. The imperfect or incomplete methods employed by Liebermeister[1] and by Leyden[2] in determining the heat production of human beings in fever justify the inference that this production is increased, and, apparently, as a rule, to a greater extent than in animals, but they do not warrant positive conclusions as to the quantity of heat produced.

We turn now to the results regarding febrile production of heat obtained by what has sometimes been called indirect calorimetry. Inasmuch as the heat energy of the body is the result of chemical changes of its proteids, fats, and carbohydrates, it is evident that if we know the kind and the amount and the heat value of the substances consumed in a given time within the body, we can compute their heat production.[3] These chemical changes, so far as their final products are concerned, are processes of oxidation. The heat values of the substances consumed in the body were determined first by Frankland and more recently with accuracy by von Rechenberg, Danilewsky, and Rubner. The investigations of Pettenkofer and Voit have shown that in hunger almost exclusively fats and proteids are oxidized, and that in this condition by determining the amount of oxygen absorbed and of nitrogen and of carbon excreted, we can estimate the

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[1] Liebermeister: Handb. d. Path. u. Therap. d. Fiebers. Leipzig, 1875.

[2] Leyden: Deutsches Arch. f. klin. Med., Bd. 5.

[3] The energy resulting from these chemical changes appears partly in the form of heat and partly in mechanical work. As practically all of the internal mechanical work is transformed within the body into heat energy, it is only the external mechanical work which is to be considered in estimating the actual heat production. The influence of this factor in fever will be spoken of later.

quantity of fat and of proteid substances oxidized during the period of observation.

Physicians of past centuries regarded increased consumption of the material of the body in fever as so evident that it needed no especial demonstration, and after Lavoisier made apparent the sources of animal heat, it was accepted almost unquestioningly until the last quarter of a century that fever is essentially a process of increased combustion or oxidation. The immense historical importance of the promulgation in 1863 of Traube's theory, which denied the dependence of fever upon increased production of heat, is that this theory has led to a careful inquiry into the grounds of beliefs hitherto generally accepted, and to the demonstration of the unsatisfactory nature of the evidence hitherto thought to be conclusive.

The striking loss of weight of most fever patients is, as is well known, a fact of great clinical importance. Weber and Finkler have demonstrated that animals in fever lose weight more rapidly than healthy animals in hunger, and although observations on human beings with reference to this point are not concordant in their results, there can be little doubt that the tendency of fever is to cause a greater loss of weight than can be explained simply by insufficient nutriment. This tendency, however, may be masked by the retention of water within the body as the investigations of Leyden and others have shown. While, therefore, the studies of the loss of weight in fever leave no doubt that there is increased destruction of tissue in this condition, we cannot consider this loss as an accurate measure of the increased destruction, nor, without further knowledge, as an indication of increased oxidation, still less as proof of excessive production of heat.

It was for a long time believed that the excessive excretion of urea in fever afforded satisfactory evidence of increased oxidation and of greater production of heat. We

now know, especially from the researches of A. Fränkel,[1] that this is so far from being true that we could explain the excessive elimination of urea better upon the assumption of diminished than of increased oxidation of tissue. In certain pathological conditions, notably phosphorus poisoning, the amount of urea excreted may be increased more than threefold, nothwithstanding, or, as Fränkel believes, in consequence of diminished absorption of oxygen and elimination of carbonic acid. It can, moreover, be computed that even without any diminution of the respiratory gases the discharge of urea may be increased without greater production of heat. While, therefore, the enormous increase in the discharge of urea in fever sheds valuable light upon a most obscure subject, the nature of febrile metabolism, it does not, regarded by itself, afford us any information as to the production of heat.

Failing to find satisfactory proof of increased oxidation in the loss of weight of the body, or the excessive excretion of urea in fever, attention was then directed to the elimination of carbonic acid, an excretory product which bears a much closer relation to the production of heat than does urea. Immense importance has been justly attached to the determination of the amount of carbonic acid excreted by an individual in fever. No point in the whole battle-ground of fever pathology has been more hotly contested than whether increased production of carbonic acid is an essential part of the febrile process. The first investigators of this question, Leyden, Liebermeister, Senator, contented themselves with the determination of the amount of carbonic acid eliminated by an individual in fever and in apyrexia. There are several considerations which greatly diminish the value to be attached to the mere estimation of carbonic acid excreted without simultaneous determination of the

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[1] Fränkel: Virchow's Archiv, Bd. 67.

amount of oxygen absorbed. As has been urged by Senator, and with especial clearness by Pflüger, increased discharge of carbonic acid does not necessarily imply increased production of the same. The discharge of carbonic acid varies, independently of its production, with the rhythm and depth of respiration, and with the temperature and the alkalinity of the blood, all factors which are altered in fever in such a manner as to favor increased liberation of carbonic acid. It is true that the influence of these factors would cause increased discharge of carbonic acid out of proportion to its production only for a limited period, and that the prolonged increase in the amount of carbonic acid discharged in fever, which has been found by several observers, can hardly be interpreted otherwise than in favor of increased production. There is another point which detracts still further from the value of exclusive determinations of the quantity of carbonic acid discharged, and this is that it makes a great difference, so far as the production of heat is concerned, whether the carbonic acid is the result of oxidation of carbohydrates, of fats, or of proteids, a difference amounting, according to Rubner,[1] to 29.5 per cent.; or, if only the proteids and fats be considered, to over 20 per cent. In investigations of nutrition it is now known to be of the utmost importance to determine the so-called respiratory quotient—that is, the ratio between the amount of carbonic acid discharged and that of oxygen absorbed. This quotient varies in a definite way with the kind of material oxidized in the body, and an accurate knowledge of it would enable us to draw conclusions as to the substances consumed in fever.

The investigations which have been published within the last few years upon the absorption of oxygen, as well as the discharge of carbonic acid in fever, are to be ranked as most valuable contributions to our knowledge

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[1] Rubner: Zeitschrift f. Biologie, Bd. xxi.

of the subject. The first determination by trustworthy methods of the amount of oxygen absorbed and of carbonic acid excreted in fever was made in Pflüger's laboratory by Colasanti upon a guinea-pig, and was published in 1877. Since that time two careful and elaborate researches upon this subject have been made, the one by Finkler, and the other by Lilienfeld.[1]

These experimenters found that in fever there is increase of the amount, both of oxygen absorbed and of carbonic acid excreted. Making comparison with healthy animals under the same conditions of nutrition, Colasanti found that the increase in the absorption of oxygen amounted to 18 per cent, and in the excretion of carbonic acid to 24 per cent.; Finkler, whose experiments were made also upon guinea-pigs, found, under varying conditions of external temperature, the average febrile increase of oxygen to be 13.8 per cent., and of carbonic acid 15.3 per cent., and Lilienfeld, who experimented on rabbits, found the average increase of oxygen to be 13.9 per cent. The statement of these averages gives an incomplete conception of the oxidation in fever, as they are derived from all stages of fever, and varying elevations of temperature. No constant proportion was found to exist between the height of the temperature and the amount of oxidation. On the other hand, a relation was observed between the oxidation and the stages of fever, viz., the initial stage with rising temperature, the acme with constant high temperature, and the defervescence with falling temperature. During the period of rising temperature oxidation was increased, and in this stage Finkler found the highest percentages, amounting to 36.6 per cent. in the increase of oxygen, and 37.6 of carbonic acid. There were, however, marked fluctuations in this stage, both in the temperature and the amount of

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[1] Colasanti, Pflüger's Archiv, Bd. xiv. Finkler, Ibid., Bd. xxix. Lilienfeld Ibid., Bd. xxxii.

oxidation. In the stage of constant high temperature such high percentages were not noticed, and the fluctuations were less marked. The processes of oxidation, according to Lilienfeld, are increased, on the average, less in the acme than in the initial stage of fever.[1] During defervescence of fever the increased oxidation falls, and may sink below the normal. Taking a broad view of these stages, we may say, therefore, that the periods of rising, constant, and falling temperatures in fever, correspond to periods of rising, constant, and falling oxidation, but we must bear in mind that the fluctuations in oxidation are much greater than, and bear no constant relation to, those of temperature; so that, in each period, there are times when oxidation may rise or fall most decidedly without corresponding changes of temperature.

Inasmuch as these experiments have shown that the increased excretion of carbonic acid in fever is accompanied by increased absorption of oxygen, and, as will be explained presently, that the respiratory quotient, if it changes at all, sinks, it is evident that we need not discard experiments in which only the amount of carbonic acid excreted has been estimated by good methods. The most accurate of these experiments are those of Leyden and Fränkel upon fevered dogs.[2] They found that, without exception, carbonic acid is excreted in larger amount in fever than in health under the same nutritive conditions, the excess amounting sometimes to 70 per cent., and in general being larger than in the experiments which have been previously considered. The earlier and meritorious experiments of Senator upon this point did not give uniform results, and he felt justified in concluding that there is no evidence of increased production of carbonic acid in fever. Subsequent experi-

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[1] In the period of rising temperature there was an increase of oxygen absorbed of 27 per cent., in the acme of 14.9 per cent.

[2] Leyden and Fränkel, Virchow's Archiv, Bd. 76.

ments with far more accurate methods have demonstrated the incorrectness of Senator's conclusions. It may be well to call to mind that Burdon-Sanderson's deductions, which have naturally had great influence among physicians here and abroad, were based, in great part, upon the data derived from Senator's experiments.

Hitherto, the methods employed in studying the respiratory gases of human beings in fever have not approached in accuracy those used in the experiments described. If the discordant results of Wertheim, which were obtained by methods manifestly very inaccurate, be discarded, all other investigators have observed augmented discharge of carbonic acid in fever of human beings. Leyden found an excess of 50 per cent. in the febrile discharge of carbonic acid; and Liebermeister, whose observations were made chiefly on cases of intermittent fever, found an excess of 30 to 40 per cent. in the period with rising temperature, and of 19 to 31 per cent. in the acme of the fever. During the defervescence of the fever the excess of carbonic acid discharged diminished, and sometimes wholly disappeared. In one instance, in which the determination was made during the rigor of intermittent fever, the carbonic acid excreted was two and a half times the normal amount; an excess so enormous that it was undoubtedly due, in great part, to the muscular movements which attended the chill.

Although we cannot consider these figures as absolutely accurate, they indicate clearly that in human beings, as well as in animals, fever is characterized by increased oxidation, and apparently that, as a rule, in man the excess of oxidation is greater than in the experimental fever of animals. This was to be expected, as it is difficult to produce experimentally in animals anything approaching in intensity the well-marked fevers of human beings.

As the result of these laborious researches we may consider it established that increased oxidation is a part

of the fever process. It has been claimed that this augmented oxidation is simply the result of the elevation of temperature, but it can be proven that this is not true. Pflüger has demonstrated that the processes of oxidation are more active at high than at low temperatures of the body, and he has also established the increment of oxidation which corresponds to each degree of rise of temperature. By means of these data Finkler has computed that in guinea-pigs the febrile elevation of temperature of 1° C. could cause an increase of the absorption of oxygen of only 3.3 per cent. Moreover, Lilienfeld found decided increase in the processes of oxidation before there is any marked elevation of temperature, and all the experiments have rendered it quite evident that there is no such relation in fever between the height of the temperature and the energy of oxidation, as would be expected if the augmented oxidation were merely the result of the increased temperature.

There is no reasonable doubt that the more energetic oxidation which we find to be an essential part of the process of fever indicates increased production of heat. Exactly what amount of heat production corresponds to the increased oxidation we cannot know until the kind and the quantity of substances oxidized in fever have been determined. It is to be regretted that no experiments have been made in which the amount of nitrogen excreted has been determined at the same time with the estimation of the oxygen absorbed, and of the carbonic acid discharged. These data would enable us to form some estimate, although not an accurate one, of the amount of heat production corresponding to the oxygen absorbed, unless very different laws from those in health control the oxidation processes of fever.

Mention has already been made of the importance of determining in fever the respiratory quotient, or the ratio between the carbonic acid discharged and the oxygen consumed. A few words will make this clear. It is well

known that under ordinary circumstances in health not all of the oxygen consumed reappears in the carbonic acid discharged. This indicates that a part of the oxygen absorbed is used in other oxidations than those resulting in the production of carbonic acid. According to the extent of these other oxidations, therefore, the respiratory quotient must vary. It is probable that these oxidations, of which carbonic acid is not a product, result at least in part, in the formation of water, which is, therefore, one of the excretory products of the body, as has been urged especially by Austin Flint. The influence of various circumstances upon the respiratory quotient has been studied, but what especially concerns us here is that in hunger this quotient sinks, which is to be expected from the fact that in this condition almost exclusively fats and proteids are oxidized. We evidently possess in the determination of the ratio of carbonic acid discharged to the oxygen consumed a means of reaching a conclusion as to a cardinal point in the pathology of fever, viz., whether the processes of oxidation in fever conform to the laws which govern them in health, and particularly whether, as has been often asserted, unusual or incomplete products of oxidation are formed to any considerable extent in fever. Colasanti and Lilienfeld found that the respiratory quotient in their fevered animals did not vary from that of healthy animals under similar nutritive conditions. Finkler observed that the respiratory quotient fell in fever somewhat more rapidly than in hunger, and this he explains by the more active oxidation in fever. All three experimenters reached the conclusion that the substances oxidized are the same in fever as in health, and that other than the normal products of combustion are not formed in fever in any considerable amount. That the metabolism in fever does differ in at least one important respect from that in hunger, is evident from the excessive amount of urea excreted in fever, but considerable variations in the disintegration of albuminous

material may occur without much change in the respiratory quotient.

The only determinations of the febrile consumption of oxygen and discharge of carbonic acid in man are those of Wertheim and of Regnard. Both investigators found a decided diminution of the respiratory quotient. The method employed by Wertheim was so defective that no confidence can be placed in his results. The experiments of Regnard[1] are presented with great neatness, but his results on other points differ so much from those obtained by trustworthy physiologists and by better methods, that we cannot accept his conclusions as to the respiratory quotient in fever without confirmation. Regnard found in all fevers which he studied a most marked diminution of the respiratory quotient. If this were true it would follow that in fever a much larger part than in health of the oxygen consumed is employed in other oxidations than those yielding carbonic acid. This would confirm the widely accepted belief that water and products of incomplete oxidation are formed in excessive amount in fever.

From the unfortunate discrepancy of these results it is evident that the knowledge which we now possess of the processes of oxidation in fever is not sufficient to enable us to form from them an accurate estimate of the heat production. In hunger, from one-fourth to one-third of the absorbed oxygen is available for combination with hydrogen to form water, the remainder uniting with carbon to form carbonic acid (Regnault and Reiset). If in fever the same ratio exists, then the excess of heat production would be proportionate to the excess of oxygen absorbed, assuming that the substances oxidized are the same in both conditions; if, however, as Regnard's experiments indicate, a larger proportion of oxygen is available in

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[1] Regnard: Recherches Exp. sur les Variations Pathologiques des Combustions Respiratoires. Paris, 1878.

fever for the oxidation of hydrogen, then the increment of heat production would be still greater, for the same amount of oxygen produces more heat when employed in the oxidation of hydrogen than in that of carbon. It is also to be considered that the same quantities of hydrogen and of carbon in their oxidation yield varying amounts of heat according to the chemical compounds in which they are contained, and we cannot say positively whether the compounds oxidized are the same in fever as in health under like conditions of nutrition. Upon the whole the weight of evidence is in favor of the view that the excess of heat production in fever is approximately proportionate to the increase in the consumption of oxygen, but it would be rash to assert this positively. It is evident that in fever ordinarily a much smaller amount than in health of the energy resulting from chemical processes is transformed into external mechanical work, so that relatively more remains in the form of heat.

In connection with this discussion of the possibility of unusual sources of heat in fever may be mentioned an hypothesis which has been advanced with much ingenuity by Dr. Ord.[1] This hypothesis is based upon the assumption, which is probable enough, that there are in the body chemical processes in which heat energy is transformed or rendered latent. These processes are thought to be chiefly those concerned in the building up of tissue. It is argued that inasmuch as the construction of tissue is manifestly in abeyance in fever, the amount of heat in the body may be increased not only by disintegrative processes, but also by "the persistence in the form of heat of energy which should have taken another form." That these building up processes influence decidedly the amount of heat produced in the developing ovum has been demonstrated by d'Arsonval's calorimetrical determination that the egg during incubation absorbs heat,

[1] Ord: British Medical Journal, 1885, vol. ii.

notwithstanding the consumption of oxygen and the excretion of carbonic acid. This fact, which might have been predicted, certainly does not justify us in refusing to attach any calorimetrical value to the determination of the respiratory gases and the urinary nitrogen. From the little we know of these constructive processes in human beings we should infer that the amount of energy in the form of heat which they appropriate bears only a very small ratio to the total heat energy set free by heat-producing processes, so that their cessation would not bring a large increment to the heat of the body. Moreover, these constructive processes are also in abeyance, although doubtless to a less extent, in starvation, with which experimental fever is usually contrasted as regards heat production and heat loss. It is not probable that any extraordinary difference in the behavior of the processes of tissue-building in fever and in starvation can occur without affecting the respiratory quotient. For the present, therefore, we cannot attach any great importance, so far as the increase of heat energy in fever is concerned to the inactivity of heat-absorbing processes.

We have gone over now the evidence which, in my judgment, establishes the fact that there is increased production of heat in fever. The same conclusion is reached also by the study of the loss of heat from the body in fever. That fever is accompanied by increased production of heat and by more active combustion, has been in all ages the belief of the majority of physicians. This belief, however, has been rather instinctive than based upon actual demonstration. It has been contested by investigators of great ability, and on the ground of scientific observation. For these reasons, and on account of the importance of the subject, it has seemed to me desirable to present to you the exact evidence, although many of its details, I fear, may have wearied you. We have learned, moreover, certain facts concerning febrile thermogenesis which the mere observation of fever patients

does not render so apparent. We have found that there is no definite relation between heat production and the height of the temperature, so that we may have excessive thermogenesis with low as well as with high temperatures. There appears to be, however, a relation between the stages of fever and heat production, this being in spite of remarkable fluctuations greatest in the initial stage, and least in defervescence.

Although for reasons which have been mentioned, and others might have been adduced, we can attach hardly an approximative value to figures which purport to give the actual heat production in fever, still, unless far more serious errors than seems possible inhere in the methods of direct and of indirect calorimetry, we can draw one important conclusion. This is that while an individual in fever produces more heat than he would in health under similar conditions as to food and muscular movements, he does not produce necessarily in fever more heat than he would in health on a full diet. And it is certain that he usually produces far less heat in fever than he often does under circumstances which normally increase heat production, such as a cool environment and muscular exercise. That one in health, with little or no change of temperature, may produce twice or more the quantity of heat which he produces in fever, makes it plain that it is impossible to explain febrile rise of temperature simply on the basis of increased thermogenesis, or what probably comes to the same thing, of increased oxidation. That in health vastly increased heat production may occur with comparatively little change of temperature is, of course, due to the fact that the dissipation of heat is proportionately increased. It is self-evident, and, so far as I know, has never been disputed that in fever the equilibrium is so disturbed that heat loss does not correspond to heat production as it should in health. This disturbance of equilibrium can be brought about in various ways, and it is only by the determination of the

actual heat production and heat loss in fever that we can say in what direction the balance is disturbed.

We have found that the production of heat is increased in fever when the comparison is made with like conditions of nourishment and of environment. It is obvious that the total loss of heat cannot equal the total production of heat during the period of febrile rise of temperature.

As is well known, most of the heat of the body is liberated from the skin and from the lungs; from the former by radiation and conduction and by the evaporation of moisture, and from the latter by evaporation of moisture and warming the respired air. It has been estimated that in man about eighty per cent. of the total heat dissipation is from the skin.

The method of direct calorimetry, already described, has been applied only to animals for the determination of the total heat loss in fever. Here Wood's experiments are the best which we possess. Leyden and Liebermeister have furnished calorimetrical data which, although unsatisfactory in many respects, indicate the general direction of febrile heat loss in human beings. All of these experiments show that more heat is dissipated in fever than under like conditions in health. The fluctuations of heat loss during a febrile paroxysm are so great that the statement of an average for the entire period has little significance. Such an average, according to Wood's results on fevered dogs, would fall between twenty to thirty per cent. excess of heat loss as compared with the loss in health under like conditions of food. The dissipation of heat in fever, however, may be at times more than double the normal amount, and again may sink below the norm. We have not sufficiently accurate estimates either of the total amount of heat produced or of that dissipated during a febrile attack to enable us to strike a balance between the two. Some persons have been so impressed with the large amount of heat lost during certain periods of fever,

that they have concluded that there must be far greater excess of heat production than previous investigations have shown to be probable. They suggest that there are sources of febrile heat of which at present we have no idea. Such conclusions seem to me quite unwarranted, when we consider the behavior of heat-loss, not for a limited time but throughout the different stages of a paroxysm of fever. We have already seen that we obtain no satisfactory conception of febrile production of heat unless we follow it during the stages of fever, and this is no less true of heat dissipation. The observation of the condition of the skin as regards temperature and moisture must in all ages have afforded an insight into the general behavior of heat dissipation during the different periods of fever. It does not require any instruments of precision to make plain the fact that a cold, dry skin, such as we observe during a febrile chill, liberates less heat than normal, or that a hot, moist skin, such as we are likely to find at the defervescence, loses more heat than normal. Not quite so evident is the direction of heat loss during the hot stage or acme of a febrile paroxysm or fastigium of a continued fever. Here the skin usually appears hot and dry. The ordinary impression that more heat than normal is dissipated during this stage is supported by calorimetrical experiments. There can be no doubt that the elevation of the cutaneous temperature which we observe in the hot stage of fever causes an increase in the amount of heat lost by radiation and conduction. Similar elevations of cutaneous temperature in health, such as those caused by muscular exercise, are accompanied by increased moisture of the surface. Not only is visible perspiration usually absent during the hot stage of fever, but the invisible perspiration is, as a rule, relatively although not absolutely diminished, as Leyden has shown. The dryness of the skin, therefore, is a factor which in the hot stage of a fever tends to lessen heat dissipation. Clinical observation, however, shows that fevers

differ markedly from each other as regards perspiration during the hot stage, the skin being sometimes bathed in perspiration without any depression of temperature. It would undoubtedly be of great interest to possess trustworthy data as to the exact loss of water from the surface of the body in different fevers and at different stages of fever. We cannot place much reliance upon the indications afforded by Weyrich's hygrometer, which has been repeatedly used for this purpose. More is to be expected from the method employed by Peiper[1] in studying insensible perspiration under physiological conditions.

The general impressions regarding febrile loss of heat derived from clinical observations, are supported by calorimetrical experiments. The dissipation of heat is least during the initial stage of fever, and greatest during the period of defervescence. During the hot stage or fastigium heat dissipation exceeds the normal, but usually, on account of the dryness of the skin, not so much as one might infer simply from the impression of heat received by the hand when placed upon the skin.

During the initial period the loss of heat, although on the average less than in the following stages, is usually greater than normal. If, however, the rise of temperature be rapid the heat loss falls below the normal amount. As there is now increased production of heat, there is evidently a glaring disproportion between the two factors, heat production and heat loss, and under these circumstances the febrile attack is likely to be ushered in by a chill. During the febrile chill all the efforts of nature combine to produce in the shortest time the greatest possible elevation of temperature. Not only is heat loss reduced to a minimum, but heat production is excited to the utmost.

During the period of defervescence, on the other hand, the relation between heat loss and heat production is reversed. This is, of course, most apparent when the fever

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[1] Peiper: Zeitschr. f. klin. Med., Bd. 12.

terminates by crisis with rapid fall of temperature. Then the loss of heat is excessive, being sometimes threefold that in the normal state, and the production is relatively and often absolutely diminished.

It is of importance to remember that there are continual and irregular fluctuations in the dissipation of heat during the different stages of fever. These fluctuations bear no definite relation either to the momentary production of heat, or to the height of the internal temperature. We deal in ordinary life so much more with units of temperature than with units of heat that it is difficult for us to keep constantly in mind the fact that no inference can be drawn as to the height of the internal temperature from the knowledge of the momentary heat production and heat loss. If the heat loss fall behind heat production the temperature of the body rises, and it can remain at this elevated point with either diminished or increased heat production so long as the heat loss equals heat production.

No correct conception of the condition of the heat-regulating mechanism in fever can be obtained without taking into consideration these irregular variations in the discharge of heat, and it is a merit of Senator and his pupils to have emphasized particularly this point. These variations are made apparent not only by calorimetric measurements and direct observation, but also by the studies which have been made of the cutaneous temperature in comparison with the internal temperature in fever. Hankel's law that the difference between the temperature in the axilla and that of the surface of the body in the febrile condition is less than in the normal condition manifestly does not hold for the chill, in which it has been proven that the superficial temperature falls while the internal temperature rises. Jacobson, Wegscheider, Schülein,[1] find that there constantly occur in the course

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[1] Jacobson: Virchow's Archiv, Bd. 65. Schülein: Ibid., Bd. 66. Wegscheider: Ibid., Bd. 68.

of most fevers changes of the superficial temperature, which stand in no relation whatever to alterations of the internal temperature. Schülein thinks that he has discovered some facts in this regard which are available in diagnosis. However this may be, these observations indicate that contraction and dilatation of the cutaneous vessels are constantly occurring, and without any regularity, in fever. These irregular variations in the calibre of the bloodvessels are also apparent to the eye in the vessels of the rabbit's ear during fever. When it is considered, furthermore, that these irregularities of cutaneous circulation vary decidedly in different situations, no further proof is needed that the mechanism which regulates the discharge of heat from the surface of the body is profoundly disturbed in fever.

These alterations in cutaneous circulation are such striking phenomena that it is perhaps not surprising that two great medical authorities should have based upon them exclusively theories of fever, Traube assuming excitation and Marey paralysis of vaso-motor nerves as the primal element in fever. We need not discuss these theories, now generally abandoned in their exclusive form. From what has been said concerning the loss or heat in fever, it is evident that we cannot explain febrile rise of temperature solely by the behavior of heat dissipation any more than we can explain it solely on the basis of increased heat production. In rejecting Traube's theory that fever is the result solely of retention of heat we must still recognize the fact that decrease in the dissipation of heat, at times absolute, at other periods relative, is a factor of the utmost importance in the febrile process.

From whatever point of view we consider the question we cannot avoid the conclusion that it is the mechanism which controls the relation of heat production to heat loss, which is disturbed in fever.

Heat production is increased in fever, but if the regu-

lating mechanism were normal, then the discharge of heat would be proportionately increased and the temperature would not be materially affected. Nor would the force of this argument be changed if febrile thermogenesis were twice as energetic as we suppose it to be.

The loss of heat is increased in fever, so that on this ground alone we should be obliged to assume increased heat production. But, even if it were proven that heat dissipation is diminished, as has been recently claimed again by Rosenthal,[1] and that fever is the result of heat retention alone, it would still be necessary to admit that the regulating mechanism is at fault, for Pflüger has demonstrated that when this is normal, changes in the temperature of the skin are attended by such changes in heat production that the internal temperature remains within wide limits unaltered.

I repeat then that the conclusion is forced upon us that the fever-producing agents must act either directly or indirectly upon the mechanism regulating the harmonious relation of heat loss to heat production.

That the heat-regulating mechanism, although profoundly disturbed, is not entirely paralyzed in fever, is proven by the effect of heat and cold upon fevered individuals. Although Colasanti believed that his fevered guinea-pig had lost all power of heat regulation under varying external temperatures, a similar conclusion has not been reached by others who have investigated this question.

We can best describe the condition of heat regulation in fever as unstable or ataxic. External cold stimulates to some extent the heat production of an individual in fever, but by no means as much as it does in health. A person in fever is not able to maintain his bodily temperature under the influence of heat and cold to the same degree that he can under normal conditions. Lieber-

[1] Rosenthal: Deutsche med. Wochenschrift, 1888.

meister, as is well known, held that heat regulation in fever is simply adjusted for a higher point, although he admits not perfectly adjusted. Experience shows that this so-called adjustment is so unstable that it does not seem proper to compare it with that to normal temperatures in health, so that it is not clear what deep meaning lies in Liebermeister's idea.

We cannot imagine the heat-regulating mechanism to be other than a nervous one.

Some years ago this was about as far as the theory of the mechanism of fever could be carried. All paths led to this mysterious nervous apparatus, and beyond this nearly all was speculation. We stood, as has been said, before imposing processes veiled in the deepest obscurity. Since then the veil has been lifted here and there and we have caught glimpses of the nature of these processes. I refer particularly to the results of researches which have brought to light a more immediate and direct dependence upon nerve energy, than had been supposed, of chemical processes concerned in the disintegration and construction of tissue, and, therefore, in the production of heat.

With one side of the nervous mechanism concerned in temperature regulation, the classical investigations of Claude Bernard have made us tolerably familiar. This is the vaso-motor nervous apparatus presiding over the circulation of blood in the superficial parts of the body, and thereby controlling in great measure the discharge of heat. That the important part taken by the perspiration in the dissipation of heat is likewise under nervous influence, has been demonstrated by Luchsinger. The facts concerning this side of the regulation of heat are too well known to require elucidation on this occasion.

Heat regulation, however, is effected not only by variations in the elimination of heat, but also by changes in the production of heat. Familiar as the fact is, it can never cease to arouse our admiration that the temperature of the body remains the same in cold and in warm

atmospheres. Man has become so dependent upon clothing that in the naked condition his capacity of preserving his normal temperature in a cold environment is much less than that of most animals. Pflüger has demonstrated that the heat regulation under varying external temperatures is accomplished by changes both in heat production and in heat loss, so that in a cold atmosphere more heat is produced and in a warm atmosphere less heat, provided the external temperature is not so high or so low as to make it physically impossible to preserve the body temperature. It is evident that this is the most rational and economical method of retaining the internal temperature of the body. To regulate the body temperature simply by variations in the discharge of heat, as was formerly supposed to be the method, would be, as has been said, like regulating the temperature of our rooms summer and winter by opening and shutting the windows without controlling the source of heat.

A heat-producing or thermogenic apparatus, therefore, is no less a part of the heat-regulating mechanism than is the heat-discharging or thermolytic apparatus, to use the terms employed by Foster. As the thermogenic apparatus is less generally understood it is not permissible to dismiss its physiology in this connection so briefly as I have the thermolytic, although our knowledge of the former is very imperfect.

I can assume that the convincing reasons are known to you which have led physiologists to conclude that most of the animal heat is produced in the muscles and the glands, and that the muscles have the larger share in this function. It is also well known that stimulation of secretory and motor nerves causes not only visible physical alterations in the glands and muscles, but also production of heat. This sort of dependence of heat production upon innervation has been long admitted. It may, however, not be so generally known that there are

reasons to believe that nervous impulses control chemical changes which result in the production of heat independently of visible physical alterations of the tissues; in other words, that heat production or thermogenesis is at least in considerable part under the immediate and direct control of the nervous system. The idea is not a new one, and was advocated especially by Claude Bernard. Recent discoveries, however, have given it unexpected support.

This subject of the relation of innervation to thermogenesis is most pertinent to the pathology of fever, but it is essentially a physiological one, and as I wish to confine to a single lecture what I have to say concerning the theory of fever, it is impossible for me to do more than summarize the most essential points belonging here. This I can do the more readily as Dr. MacAlister,[1] in his admirable Goulstonian Lectures on the "Nature of Fever," which were delivered last year, has clearly and forcibly presented the main facts.

The larger part of these facts relate to the chemical changes and heat production of muscles under varying conditions.

That a large part of the chemical changes in a muscle in the condition which we call repose is under the influence of the nervous system, is made apparent by the great diminution in its consumption of oxygen and formation of carbonic acid, which follows the separation of the muscle from all connection with the central nervous system. This is conclusively shown by the experiments of Bernard, Pflüger, von Frey, and others. It is, of course, possible, and it has generally been supposed that under these circumstances it is simply the withdrawal of motor impulses which lowers the heat-producing energy of the muscle.

Far more suggestive as regards the point under consid-

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[1] MacAlister: The Lancet, 1887, vol 1.

eration are the results of investigations which have been carried on in Ludwig's laboratory by Meade Smith, MacAlister, and Lukjanow. These experimenters have shown that heat production and contraction are in a measure independent properties of the muscle. By various influences the thermogenic property may be so impaired that a stimulus causes contraction with scarcely any development of heat. The laws governing the restoration and the fatigue of the thermogenic function differ from those controlling the mechanical function. These researches, upon which I here only touch, have made it extremely probable that there are in the muscle chemical processes resulting mainly in the production of heat and chemical processes causing mainly contraction, and that these processes, although coördinate, are not identical. A new light is shed upon the meaning of the term chemical tonus of muscle, which has for some time been used by some physiologists. Great caution is properly exercised by Ludwig and his pupils in the interpretation of these interesting results. They do not infer from them, necessarily, the existence of so-called thermic or calorific nerves. They suggest that it is possible to explain the phenomena upon the supposition that there are in the muscle two kinds of material, thermogenic and contractile, and the nervous impulses acting upon these may pass through the same set of nerves.

Proof of the existence in connection with muscles of thermic in distinction from motor nerves, would be afforded if we could succeed, after paralysis of the motor nerves, in exciting by nerve stimulation the thermogenic function of the muscle. We possess, in curare, a drug which paralyzes the terminations of the motor nerves. Meade Smith attempted by its aid to determine whether possible thermic nerves may be differentiated from motor, but he reached no positive conclusion on this point. There are, however, on record some observations which suggest the possibility that in moderate doses curare may leave intact thermic

nerves after the suspension of the function of motor nerves. When an animal is profoundly under the influence of curare the internal temperature falls, and the processes of oxidation are greatly reduced. The animal is no longer able to resist the changes of external temperature, its own temperature rising and falling like that of a cold-blooded animal when exposed to heat or cold. This effect of curare poisoning is another proof of the dependence of heat production upon nervous influences. Claude Bernard in his early researches on the action of curare noted elevation of temperature soon after its administration. Voison and Lionville[1] observed after subcutaneous injections of curare in man rigors, perspiration, headache, and elevation of temperature to 104.7° F. They attribute to curare the power of producing all of the essential phenomena of fever. Fleischer[2] noticed in dogs and in rabbits rise of temperature after curare injections, and the same was observed in a rabbit in one case by Högyes.[3] Recently Mosso[4] claims that an animal may be placed so far under the influence of curare as to paralyze completely the voluntary muscles, and the internal temperature either remain normal or rise. He infers that these moderate doses of curare, although sufficient to paralyze the motor nerves, must have left intact the thermic nerves. That rise of internal temperature is not due to retention of heat, he thinks is evident from the normal or elevated temperature of the skin. Mosso is strengthened still further in his conclusion as to the existence of thermic nerves, by finding that after complete paralysis of the motor nerves by curare injections of strychnine cause an elevation of rectal temperature, which may amount to three degrees centigrade. Under

[1] Virchow and Lionville: Virchow u. Hirsch's "Jahresbericht," 1886, I. p. 330.

[2] Fleischer: Pflüger's Archiv, Bd. ii. p. 441.

[3] Högyes: Arch. f. exp. Path. u. Pharm., Bd. xiv. p. 136.

[4] Mosso: Virchow's Archiv, Bd. 106.

these circumstances strychnine produces no spasms or other visible mechanical effect upon the muscles. Mosso brings forward a number of other experiments (decidedly open to criticism) intended to demonstrate the existence of nerves directly controlling heat production, but those which I have mentioned are by far the most striking. It seems to me that the natural interpretation of these experiments is in favor of the view that there are nerves controlling heat production in the muscle distinct from motor nerves. Far more conclusive as to this point than thermometric observations would be calorimetric experiments determining the heat production of animals under varying doses of curare.

This whole line of experimentation directed toward the differentiation of the mechanical and the chemical functions of muscle is certainly most suggestive, but so long as the interpretation of the results is not perfectly clear, we should be very guarded in drawing far-reaching conclusions. I cannot refrain, however, from pointing out that, as mentioned by MacAlister, all of these thermogenic phenomena may be found eventually to depend upon nerves whose chief function, on the one hand, is the disintegration, the metabolism of tissue, and, on the other hand, the restoration, the anabolism of tissue. From the study of the electrical changes which stimulation of the pneumogastric nerve produces in the heart muscle, Gaskell concludes that this nerve puts the heart in a condition of relative rest during which the energy of the muscle is increased. During this period there is reason to believe that the material of the muscle, which, when disintegrated, gives rise to heat and mechanical work, is in the process of restoration. Hence Gaskell speaks of the pneumogastric or inhibitory nerve of the heart as anabolic—that is, it directs the restorative, formative, anabolic processes in the muscle. On the other hand, the accelerator nerve of the heart induces the opposite electrical changes in the heart muscle. Gaskell describes

this nerve as katabolic—that is, its stimulation causes disintegration of the muscle materials, and liberates energy in the form of heat and of mechanical work. If it be found that similar inhibitory and accelerator nerves preside over the chemical changes in the voluntary muscles and other tissues of the body, then Gaskell's induction as to the existence of anabolic and katabolic nerves must be regarded as one of the most important and profound in modern physiology. Thermo-excitory nerves we should then rank as katabolic, thermo-inhibitory as anabolic.

These investigations tending to demonstrate the independent existence of thermogenic properties in the muscles and possibly of nerves directly controlling thermogenesis, have prepared us for the consideration of the relation of the central nervous system to the heat-producing properties of the body. Here you will willingly permit me to confine my remarks to the more essential and best established facts, without entering into a full discussion of one of the most perplexing subjects in the physiology of the nervous system.

The clinical basis of the doctrine that lesions of the central nervous system influence directly the temperature of the body was laid by Sir Benjamin Brodie, who reported the well-known case of fracture of the cervical vertebræ and injury of the spinal cord followed within a few hours by a rise of temperature to 111° F. measured between the scrotum and the thigh. Since then many similar instances have been reported. It is well to remember, in framing theories on the basis of these cases, that there are also on record not a few instances in which apparently similar injuries of the same parts of the spinal cord have been followed by equally striking fall of temperature.

The experimental basis for the acceptance of an influence of the nervous system on temperature was laid by Bernard, in his celebrated experiments on the effects

of division of the sympathetic nerve in the neck. Bernard interpreted the increased temperature of the ear following this operation as referable not only to the larger amount of blood in the part, but also to increased tissue metamorphosis and consequent heightened heat production. The latter part of this interpretation is not generally accepted. It may be said here that the common idea that an organ or tissue simply because it receives a larger supply of blood indulges in more active metabolism is opposed by the investigations of Pflüger, who finds that the amount of oxygen taken up by the cells depends in a far higher degree upon the state of their innervation at the time than it does upon the supply of oxygen. The demand of the tissues for oxygen is not increased simply because the supply is greater. The arguments upon which Pflüger bases this line of reasoning, although not without opposition, would dispose of the idea that when any considerable increase of heat production in the muscles occurs this can be explained simply by vasomotor changes. I mention this here, because the opinion has been advanced that a large part of the increased production of heat in fever and after certain injuries to the nervous system is referable simply to vasomotor changes in the muscles.

In 1866 Tscheschichin[1] published experiments which he interpreted as indicating the existence in the brain of centres which, when irritated, moderate the production of heat, and which he called heat-moderating or heat-inhibitory centres, and in the spinal cord of centres which when stimulated excite the production of heat, heat-excitive centres. These conclusions were not justified by the experiments, but they have been widely accepted.

I may here say that, in this connection, I use the term heat centre as a convenient and generally adopted one. There is a proper reaction against the prevailing misuse

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[1] Tscheschichin: Reichert und Du Bois-Reymond's Archiv, 1866.

of the word centre for all sorts of little understood localization of nervous functions. It would undoubtedly be more accurate to use some such expression as thermically active region instead of heat centre.

It is not easy to reconcile the clinical fact that in human beings lesions of the spinal cord may be followed at once, or in a very short time, by extraordinary elevations of temperature with the results of experiments on animals. That the rise of temperature in human beings is not due to inflammatory fever is apparent from the rapidity with which it follows the injury. It cannot be explained by vasomotor lesions, for the paralysis of the vasomotor nerves accelerates the discharge of heat from the surface of the body. The high temperature can be explained on Tscheschichin's assumption. The lesion either stimulates the spinal thermogenic centres or removes the influence of the thermo-inhibitory centres. These clinical observations are the strongest support which has been found for the belief in the existence of centres in the spinal cord which accelerate heat production. Complete section of the cervical part of the spinal cord in a dog or a rabbit is, under ordinary conditions, always followed by a rapid fall of the internal temperature and diminished oxidation. These varying results in man and in animals have been explained by supposing that after section of the cervical cord, on the one hand, the discharge of heat is increased by dilatation of the superficial bloodvessels, in consequence of vasomotor paralysis; and, on the other hand, the production of heat is increased by withdrawal of thermo-inhibitory cerebral impulses. If, as ordinarily happens in dogs and smaller animals, the first factor predominates, then, in consequence of sinking of the internal temperature, the heat-producing processes are so reduced that the influence of the second factor is not manifest. The attempt has been made to test this explanation by placing the animal in a warm atmosphere. If thereby the heat discharge be

reduced to a minimum, it is found that the internal temperature of the animal often rises more rapidly than that of a normal one under the same external conditions. Here thermometric observations are not conclusive as to the point to be tested, for the more rapid rise can be explained simply by failure of the heat-regulating mechanism. Wood's calorimetric experiments seem to show that there is greater heat production, under these circumstances, in the animal with cut cord. These experiments admit of various interpretations, but if they be regarded as establishing the assumption from which we started, then it is evident that in man and in large animals the increased heat production after injury of the cord would not be so readily overcome by the increased discharge of heat from the surface, for, in proportion to its volume, a large animal has less surface than a small one. The interplay, therefore, of these opposing tendencies might cause different results, according to the size of the animals.

Tscheschichin found that a transverse section made at the junction of the pons and medulla oblongata is followed, in a short time, by rise of internal temperature. As the superficial temperature is also elevated, he concludes that there is no retention of heat; moreover, the section is made above the dominant vasomotor centre. Wood has shown by means of the calorimeter that after this operation there is actual increase in the production of heat. He, as well as Tscheschichin, interprets the experiment as indicating thermo-inhibitory centres above the lower border of the pons. Bruck and Günter[1] repeated and modified these experiments under Heidenhain's directions. Out of seven cases in which they separated the pons from the medulla, they observed in only two rise of temperature; of eleven cases in which they punctured the pons with a needle, in five they noted increased temperature. Heidenhain thinks these experi-

[1] Bruck and Günter: Pflüger's Archiv, Bd. iii.

ments indicate heat-exciting rather than heat-moderating centres, and it must be admitted that the evidence is not conclusive in support of either view.

By far the most interesting and conclusive experiments, showing the influence of the central nervous system on thermogenesis are those of Isaac Ott, followed by Richet, Aronsohn and Sachs, Baginsky, and Girard.[1] The observations of Ott, Richet, and Aronsohn and Sachs were made independently and at about the same time, but Ott was the pioneer. The experiments of Aronsohn and Sachs are reported with especial fulness and detail. These investigators found that if the skull of a rabbit be trephined at the junction of the coronal and sagittal suture, and a needle be passed vertically down so as to puncture the anterior part of the caudate nucleus near its median convexity, there follows a rise of temperature, which may amount to three degrees or more, and which may persist for two or three days. The rapidity and the duration of this elevation of temperature vary somewhat with the depth of the puncture, parts immediately beneath the caudate nucleus being also thermically active. Puncture of the overlying cortex or medullary substance has no such effect upon temperature. With the exception of some increase in the frequency of the respiration and of the pulse, the animal after puncture of the anterior median part of the caudate nucleus presents no abnormal symptom other than the rise of temperature.

I have several times repeated this experiment and always with the result described. That the pyrexia induced by puncture of the caudate nucleus is not due to vasomotor changes causing retention of heat, is proven

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[1] Ott: Journal of Nervous and Mental Diseases, April, 1884; MEDICAL NEWS, July, 1885. Therapeutic Gazette, Sept. 1887. Richet: Arch. de Phys., 1884. Aronsohn and Sachs: Pflüger's Archiv, Bd. 37. Baginsky and Lehman, Virchow's Archiv, Bd. 106. Girard: Arch. de Phys., 1886.

by Richet's and Ott's calorimetric experiments, and by the determination by Aronsohn and Sachs that the consumption of oxygen and the elimination of carbonic acid, and urinary nitrogen are increased. Aronsohn and Sachs and Girard find that electrical stimulation of the anterior median part of the caudate nucleus causes the same thermic phenomena as the puncture, and they, therefore, conclude that this region contains a thermo-excitor heat centre. This is the natural interpretation of their experiment, although Baginsky and Ott regard the centre as thermo-inhibitory on grounds which cannot be considered convincing.

Ott claims that there are four cerebral heat centres, one about the corpus striatum, the second in the caudate nucleus, the third in the anterior inner end of the optic thalamus, and the fourth near the median line between the optic thalamus and the corpus striatum. The greatest rise of temperature he found after injury of the thalamic centre.

No adequate demonstration has been afforded of any influence of the cerebral hemispheres upon thermogenesis. Corin and van Beneden[1] find that pigeons, after removal of their cerebral hemispheres, exhibit no change of temperature, no failure of the heat-regulating mechanism, and no alteration in the excretion of carbonic acid.

I have endeavored to present to you the main physiological facts bearing upon the relation of the nervous system to thermogenesis. It must be admitted that we are left to surmise as to the interpretations of many of the facts, and particularly as to their connection with each other. But certain important points come out clearly. We have found evidence of the existence in the body of chemical processes resulting chiefly in the production of heat energy. We have learned that these processes are under the direct control of the nervous

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[1] Corin and van Beneden: Arch. de Biol., 1887.

system, and possibly of nerves distinct from those now recognized as motor or secretory. We have seen that there are regions in the central nervous system which are doubtless in some way connected with these nerves, and through them control the chemical processes resulting in the production of heat.

The bearing of these facts upon the theory of fever is evident. The study of heat production and of heat loss in fever has led us, by arguments which need not be repeated, to the conclusion that the pyrogenic agent must in some way act upon the heat-regulating mechanism. The study of this mechanism, more particularly of its thermogenic side, affords some insight into the manner in which the fever-producing agent may affect the regulation of heat. The main difficulty in the neurotic theory of fever has been to understand how by any action of the fever-producing agent directly upon the nervous system the chemical processes leading to heat production could be stimulated. I have dwelt thus at length upon the innervation of thermogenesis to show that this difficulty has been in great part overcome.

To some it seems more reasonable to suppose that the pyrogenic agent circulating in the blood acts directly upon the tissues, altering and stimulating their chemical changes. This is the hæmic theory, which, in some form, has always stood over against the neurotic theory of fever. Although it may at first glance appear simpler, the hæmic theory is really the more complicated, for it has already been set forth that we cannot explain fever simply by increased heat production, so that even if the primary effect of the fever agent were upon the heat-producing processes there must be a secondary influence upon the nervous system, for heat dissipation is no less disturbed than heat production.

If an animal be thoroughly curarized so that no impulses from the nervous centres can reach the muscles, the great heat producers, then it is found to be impossible

to produce febrile elevation of temperature by the injection of pyrogenic agents. This fact, first demonstrated by Zuntz, is justly held to weigh heavily in favor of the neurotic theory of fever.

Contrary to the results of Murri,[1] I have not been able to induce rise of temperature or check its fall by the injection of pyrogenic agents into the jugular veins of dogs whose spinal cords have been cut in the lower cervical region. In these experiments I have employed various pyrogenic agents, and especially pepsin and papoid. One specimen of the latter which I used possessed very striking pyrogenic properties.

The pyrexia produced by puncture of the caudate nucleus in the manner already described, possesses all of the essential properties of fever, regarded as abnormal elevation of temperature. In this experimental condition there are increased production of heat, increased dissipation of heat, excessive elimination of urea and of carbonic acid, and excessive absorption of oxygen. The breathing and the pulse are increased in frequency. The elevation of temperature (usually after a brief fall) begins within half an hour after the puncture, attains a febrile height and persists sometimes for days. As no observations exist as to the heat regulation of these animals, I have made experiments on rabbits after puncture of the caudate nucleus, by placing them in a cold environment and in a box heated to various temperatures, and I find that their power of temperature regulation is less than that of normal animals.

These animals, in a word, present all of the essential symptoms of fever, and I do not know why we should not call the condition fever. If so, we must admit that injury to a circumscribed definite region of the brain is capable of causing fever. This experiment, therefore, is of the greatest importance in support of the

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[1] Murri: Teoria della Febbra, Fermo, 1874.

neurotic doctrine of fever. It indicates, of course, that we may have fever of purely nervous orgin, without any pyrogenic agent in the blood. This experimental evidence is supported by the clinical cases collected by White in *Guy's Hospital Reports*, 1884. It is to be hoped that by careful thermometric study of focal brain and cord lesions a more accurate idea may be reached than is now possible of the topography of the thermically active regions in the central nervous system of man.

Admitting the dependence of fever upon the nervous system, I do not regard as particularly profitable with our present knowledge the discussion as to whether febrile thermogenesis is excited by the withdrawal of thermo-inhibitory impulses or by the stimulation of thermo-excitory nerves or nerve centres. If we regard, and there are forcible arguments for doing so, possible heat-inhibitory nerves as anabolic, and the heat-exciting nerves as katabolic, then inasmuch as the formative or anabolic processes are manifestly in abeyance in fever, we can reasonably infer that the function of the heat inhibitory nerves or centres is impaired. The phenomena of the febrile chill in which both the contractile and the thermogenic properties of muscle are stimulated, speak strongly in favor of direct irritation of the heat-exciting nerves in fever. We might infer, therefore, that both sets of nerves or nerve centres are affected.

But my aim in this lecture has been not so much to construct a theory of fever, a theory which, although it may be useful, must necessarily be largely speculative if it be coherent and rounded, but to bring before you the main facts concerning heat production, heat loss, and heat regulation in fever, and to point out the physiological basis on which their solution is to be expected.

LECTURE II.

THE EFFECTS OF INCREASED TEMPERATURE OF THE BODY.

In the last lecture I endeavored to bring before you the main facts which we possess bearing upon the explanation of febrile rise of temperature. After a review of our knowledge concerning heat production, heat dissipation, and heat regulation in fever, we were led to the conclusion that neither the changes hitherto observed in the production of heat nor those in the loss of heat suffice to explain febrile temperatures. Such an explanation seemed possible only upon the assumption that the fever-producing agents act either directly or indirectly upon the nervous mechanism controlling the relations to each other of the production and the discharge of heat. We then turned our attention to the relations of the nervous system to these processes, and found that the investigations of recent years have enabled us to obtain a much clearer conception than was formerly possible, of the manner in which the complicated heat relations in fever may be brought about by an action upon the nervous system. We found even substantial experimental basis in support of clinical facts which show that circumscribed lesions of certain parts of the central nervous system may induce directly febrile disturbances of animal heat.

To carry the subject further, to consider whether pyro-

genic agents act primarily or only secondarily upon the processes concerned in heat production or upon those concerned in heat dissipation, or upon the apparatus regulating the relations to each other of these two sets of processes, to discuss whether these agents act directly upon the central nervous system, and if so upon what part; or upon the peripheral nerves or their terminations, or upon the tissues; to follow out more fully than we have done hitherto the themes here suggested would lead us with our present knowledge into a sea of speculation. We should find only here and there a faint light of fact to guide us. Even upon foundations as insecure as this speculations have their legitimate uses. A good hypothesis is a most valuable incentive to scientific work. It is not my purpose, however, to carry you with me further in this direction, although I realize that a single lecture has been far from sufficient for a thorough exposition of this subject.

After dismissing the considerations bearing upon the so-called theory of fever, there still remains a host of questions properly belonging to our subject. It is evidently impossible, even if it were desirable, that these lectures should include a discussion of all of these questions. I have, therefore, selected certain ones, partly because they seem to me of immediate interest and partly because I have given some attention to their study.

In the present lecture I wish to present to you some observations concerning the relation of elevation of temperature to other disorders of fever, and as to the question how far increased temperature is a source of danger in fever?

Here I may repeat that the word fever is used as a convenient name for a group of symptoms commonly associated together in febrile diseases. The association of these symptoms, however, is so loose that we regard only the dominant one—the increased temperature—as the essential criterion of the existence of fever. It saves cir-

cumlocution to adopt this somewhat vague and common signification of the term fever, although I think it would be an improvement to confine the term to abnormal elevation of temperature. The literature of fever is full of misapprehensions resulting from the various meanings attached to the word by different authors.

All of the bodily functions may be disordered in fevers. The various symptoms or classes of symptoms which are so commonly associated as to be regarded by many as belonging to the febrile process are, in addition to heightened temperature, increased frequency of the pulse and other circulatory disturbances, increased rapidity of respiration, muscular weakness, lessened secretions, disordered nutrition and digestion, and nervous symptoms.

What is the connection, if any, between these symptoms and the elevation of temperature? What degrees of elevated temperature are dangerous to life, and in what does the danger consist? This subject can, at least, claim the interest that attaches to the questions of the day. The various opinions which have been held by clinicians on these points are too well known to you to require an historical review. I need only remind you that until within a few years the views advocated with especial force for nearly thirty years by Liebermeister have prevailed, although not without considerable opposition. According to these views, the chief source of danger in uncomplicated essential fevers is the elevation of temperature, and the main indication for treatment is the reduction of temperature. Above all, it was urged with apparently convincing arguments that the weakness of the heart, which is undoubtedly one of the gravest dangers of fevers, is the direct effect of prolonged high temperature, and is manifested anatomically by parenchymatous or fatty degeneration of the cardiac muscle. Liebermeister sharply defined his position when he said, "A man whose temperature measures continuously 104°

(40° C.) or more surely dies in consequence of the elevation of temperature, one in a few days, another after a somewhat longer time, according to the resistance of the individual." "If his temperature reaches 108.5° (42.5° C.) or more, then is he irrecoverably lost."[1]

At the present moment there is a decided reaction against these views, a reaction which in some quarters goes to the extent not only of denying that there is danger in febrile temperatures which do not exceed a very high point, but of asserting that the elevation of temperature is a beneficent provision, a most important *vis medicatrix naturæ*, which should not be checked by the interference of the physician. This reaction of opinion is plainly due, in great part, to the disappointment which has followed the high hopes raised by the discovery of a number of drugs which are admirable antithermic agents and, nevertheless, do not exert over febrile diseases that controlling influence which had been anticipated.

These questions, you may say, are clinical ones, and not much edification is to be expected from their discussion by a pathologist. So far as the propriety of the use of antipyretic agents or of any other mode of treatment in fever is concerned, it is true that the decision must be reached at the bedside and cannot and never should be controlled by the results of experimental pathology. But an appeal has properly been made to experimental pathology to shed light upon such questions as the effects of heat upon the functions of the whole body and of its various organs, and upon the causes of parenchymatous and fatty degenerations. The arguments advanced in support of the view that all of the characteristic symptoms of fever are directly dependent upon the increase of temperature and that high temperature is the chief source of danger, are derived no less from experimental pathology than from clinical observations.

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[1] Liebermeister: Volkmann's Sammlung, No. 31, p. 240.

Three methods have been employed to determine the effects of increased temperature in fever: one is to study the effects of external heat upon man and animals; the second is to examine in different fevers and in different cases of the same fever the relation of the temperature to the other symptoms, and to the general condition of the patient; and the third is to note the influence of reduction of temperature upon these symptoms. Each method has its limitations.

The condition produced by exposure to external heat, even if it be called thermic fever, is something quite different from ordinary fevers, and we cannot transfer the results obtained by this method directly to the explanation of febrile phenomena. On the other hand, in the clinical study of fevers it is very difficult and often an arbitrary matter to separate the effects of increased temperature from those of other factors nearly always present. Hence we find no agreement of opinion among physicians as to what symptoms or lesions in fever are referable to the heightened temperature, and what are due to infectious or other conditions often present. Even the frequent or constant association of certain symptoms with elevated temperatures and their subsidence or disappearance by reduction of temperature do not justify us in inferring that the high temperature is the cause of the symptoms, for both may be coördinate effects of the same cause, and the so-called antipyretic treatment may influence other conditions as well as the temperature. As has been frequently said of late, the high temperature may be rather an index of the severity of the disease than a source of danger in itself.

In hyperpyrexia and in many cases of insolation there can be no doubt that the high temperatures, as such, are the main elements of danger. But both of these conditions have important points of distinction from ordinary febrile processes. In hyperpyrexia there is probably almost complete paralysis of heat regulation, and we shall

find that an analogous condition with similar dangers sometimes develops in animals artificially heated. The cases of insolation in which the high temperature is so dangerous are analogous to the condition which may be produced in animals by brusque elevation of the bodily temperature through exposure to heat, and which differs from that resulting from more gradual increase of temperature.

The most direct way of determining the influence of heat upon the body is to raise the internal temperature by the external application of heat. Here we are not disturbed by the presence of other factors, such as infection, which render doubtful so many of the conclusions derived from clinical observations as to the effects of high temperatures. For the solution of many problems it is evidently irrelevant whether the source of heat be within or without the body.

These experiments, if properly conducted, are calculated to shed much light upon many questions relating to the effects of febrile temperatures.

According to the testimony of all experimenters, a mammalian animal, artificially heated, dies when its internal temperature reaches 111.2° F. (44° C.) or 113° F. (45° C.). Death is preceded by convulsions and immediately or soon after death rigor mortis appears. At the moment of death the irritability of the heart and muscles ceases. Death seems to be due to heart paralysis, and the cause of this is usually set down as heat rigor, but this is not probable as death generally occurs at a temperature several degrees below that at which rigor of the heart muscle appears.

It is generally argued that temperatures several degrees below those which are fatal must exert toxic effects, and this conclusion seemed to be substantiated by the majority of experimenters, who found that animals whose temperatures were artificially raised to 105° F. (40.5° C.) or 107° F. (41.7° C.), or even to a lower point, manifested signs

of illness. These latter results, however, are opposed to those obtained by Rosenthal, and especially Naunyn,[1] who points out that the conditions in most previous experiments were not favorable, as the animals were generally placed in small, dark, poorly ventilated metallic boxes. Naunyn succeeded in keeping a rabbit alive for thirteen days with an average temperature of 106.7° F. (41.5° C.).

Following Naunyn's example, I have had constructed a wooden box, three feet long, two feet high, and two feet broad, which fits closely within a double-walled galvanized iron box. The wooden box is provided with a perforated movable bottom, which allows the urine to escape. The space between the two walls of the iron box measures three inches across, and is filled with water, which, therefore, surrounds the inner box on all sides, except at the top, which is left open. The dimensions of this apparatus are somewhat larger than those of Naunyn's heating-box. A folded woollen blanket was drawn over each end of the box, so as to leave uncovered at least one-third, and generally more of the top. A rose burner placed underneath served to heat the box. At first a thermo-regulator was employed, but this was found unnecessary, as the temperature of the room varied but little, and there was no difficulty in keeping a sufficiently constant temperature in the box. The experiments were made upon rabbits, and only a single one was placed in the box at a time. Corrected thermometers were used. The temperature of the box was taken a short distance above the bottom, and that of the rabbit at a depth of three to four inches in the rectum. This occasion does not seem an appropriate one to describe these experiments in detail with their protocols. I shall take another opportunity for that, and at present give only a general

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[1] Rosenthal: Zur Kenntniss der Wärmeregulirung u.s.w., Erlangen, 1872. Naunyn: Archiv f. exp. Path. u. Pharm., Bd. 18.

account of those results which relate to the subject before us.

In the box described I have succeeded in keeping for three weeks two large black rabbits, the one with an average rectal temperature of 107.3° F, (41.8° C.), the other with an average temperature of 106.6° F. (41.4° C.). The rectal temperature fluctuated usually between 105.5° F. (40.8° C.) and 108° F. (42.2° C.), scarcely ever sinking below 105° F. (40.5° C.), but occasionally rising as high as 109.5° F. (43.1° C.). The temperature of the box varied between 96° F. (35.5° C.) and 106° F. (41.1° C.). The rabbits lay most of the time stretched out, breathing very rapidly. They took their food greedily, and did not appear ill. At the end of the experiment the first animal was removed from the box, and appearing perfectly well for ten days afterward it was used for another experiment; the second animal was killed at the end of the experiment, and presented marked fatty degeneration of the heart, liver, and kidneys. Both animals lost weight while in the box.

In these and similar experiments the rabbits were given only moist, green fodder, and were allowed to drink plenty of water, which they took eagerly. It is important for the success of the experiment that the temperature should be gradually, and not suddenly, raised.

Different rabbits offer varying degrees of resistance to the effects of high external temperature. It has seemed to me that black and gray rabbits surpass, in this respect, white rabbits. The same temperature of the box does not produce, in all cases, the same rectal temperature in different animals, or in the same animal at different times No factor is of more importance in determining the effects of external heat than the animal's power of temperature regulation. Failure of this power is manifested by a sudden rise of internal temperature, which may quickly attain a point incompatible with life. This event may take place without any alteration in the box temperature.

The degree of internal temperature at which this paralysis of heat regulation occurs varies in different animals. One may be able to hold his temperature, for a short time, from further rise at as high a point as 109.5° F. (43.1° C.); in another, after the temperature has reached 107.6° F. (41.5° C.), there may occur, without any change in the box temperature, a sudden, and often fatal, elevation of temperature. In general, temperatures between 108° F. (42.2° C.) and 109° F. (42.8° C.) may be regarded as critical temperatures for these animals. One is forcibly reminded by these sudden and dangerous elevations of temperature of the occurrence of hyperpyrexia in certain fevers of human beings, and there is reason to believe that this, too, is caused by paralysis of heat regulation.

It seemed to me of some practical interest to determine what effect upon the rabbit's power of resisting high temperature is exerted by exhausting influences, particularly by anæmia. For this purpose rabbits which had been moderately bled, and others which had been used for some other experiments, were placed in the hot box. It was found that these animals are, although not without occasional exceptions, unmistakably less resistant to the effects of high temperatures than are robust animals. They succumb sooner, and at lower box temperatures.

We may now consider what inferences may be drawn from these and similar experiments as to the effects of high bodily temperatures. It seems clear that a considerable part of the current arguments based upon experiments concerning the injurious effects of high temperatures must be revised in the light of Naunyn's experiments, and of those which I have briefly related. Because an animal may be killed by raising its temperature to 111° F. (43.9° C.), or 113° F. (45° C), it does not follow that an increase of temperature up to within 4° or 5° F. of this fatal point involves danger to life, or even any serious disturbance of the functions of the body. Although experiments in hot-air chambers show that in

man brusque elevations of the temperature by only a few degrees give rise to serious symptoms, Krishaber[1] found that by habituation his temperature could be raised to 106.5° F. (41.4 C.), or 107.2° F. (41.8), without much discomfort. As small animals generally succumb more readily than large ones to artificial heating, it is not likely that the power of resistance in human beings is less than that found to exist in rabbits, and there is reason to believe that it is greater.

We cannot transfer directly to human beings the highest temperature at which we found rabbits can exist without serious discomfort save increased respiration. A rabbit's temperature is normally considerably higher than that of man, and apparently slight causes suffice to produce marked fluctuations. The normal rectal temperature of the rabbits used in my experiments was generally between 102° F. (38.9° C.) and 103° F. (39.4° C.). The highest average temperature at which a rabbit was kept for three weeks in the hot box exceeded, therefore, by 4° to 5° F. the average normal temperature. Such an increase would not correspond to a high febrile temperature in man. We can, however, with equal, and probably greater propriety, compare this temperature with that at which death surely occurs in a condition bordering on heat rigor. This temperature (111° to 113° F.) is probably about the same for man as for rabbits and other mammalians. From this point of view the inference may be drawn, although, of course, with much reserve, that human beings may tolerate temperatures of 107° F. (41.7° C.), or even higher, for a considerable time. This inference is supported by clinical observations, especially in cases of relapsing fever.

As already pointed out, the condition produced by artificial heating is not directly comparable with that in fever. In the former the loss of heat from the body is

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[1] Krishaber: Gaz. Méd. de Paris, 1877.

reduced to a minimum; the superficial temperature is three or more degrees higher than the internal, so that the average temperature of the whole body is higher than in fever with the same internal temperature. We cannot say, therefore, but that man may tolerate considerably higher internal temperatures when the elevation is brought about under conditions in which the discharge of heat is not checked than when the temperature is forced up by stopping heat dissipation. This would be proven if confidence could be placed in the enormous elevations of temperature reported by Teale and others. In these cases, however, even if authenticated, it is probable that heat is abnormally distributed in the body, and we cannot infer that the internal temperature is uniformly raised to such paradoxical heights.

It is of the utmost importance to bear in mind that, as my experiments have shown, not only do animals differ in their power of tolerating high temperatures of the body, but this resistance may be weakened by various depressing causes. Nothing would be more irrational than to conclude, because one individual in a certain condition can tolerate very high temperatures, another in a different condition possesses the same power. In fevers we have various factors, particularly infection, which we may well believe can lower the tolerance of high temperatures. That in some fevers, particularly relapsing fever, this does not appear, or only partially, does not disprove that in another fever, such as typhoid or pneumonia, the system may be placed by other factors of the disease in such a condition that even moderately high temperatures are injurious. It does not seem to me proper in these cases to lay, as some seem inclined to do, the sole stress upon the element of infection. This is in all likelihood the determining factor, but the practitioner cannot shut his eyes to the possibility that under its influence the high temperature, as such, is a source of danger to his patient.

With these restrictions I shall surely not be misunder-

stood when I assert that temperatures which are ranked as high febrile temperatures do not in themselves, independently of other factors, exert any such injurious influence as has been usually attributed to them.

Our attention up to this point has been directed to the effects of high temperatures upon the general condition of the body. It is of importance for the proper understanding of fever to determine the influence of heat upon the structure and functions of the various organs. To what extent can the febrile disorders of respiration, of circulation, of secretion, of nutrition, of innervation be attributed directly to the elevated temperature? These are questions which can be answered better by experimental methods than by clinical observation, for the latter has to deal with the effects of heat complicated by other circumstances whose influence cannot be accurately determined. The one method, however, should be made to control the other.

The most striking immediate effect of heat upon an animal is increased frequency of respiration. When a dog or a rabbit is placed in an atmosphere of 100° F. (37.8° C.), it at once begins to pant and the respiration may run up to 150° or more. The causation of this increased respiration, to which the name heat dyspnœa has been applied by Ackermann,[1] has been repeatedly investigated. Goldstein[2] in Fick's laboratory found that by applying to the carotid arteries tubes through which hot water is flowing the respirations may be greatly increased in frequency. Goldstein's experiment is usually cited as the crucial one, showing that the increased breathing is due to the effect of the heated blood upon the respiratory centres in the medulla oblongata. Sihler,[3] working in

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[1] Ackermann: Deutsches Archiv f. klin. Med., Bd. ii.

[2] Goldstein: Würzburger Verhandl., 1871.

[3] Sihler: Journal of Physiology, vol. ii., and Studies from the Biological Laboratory, Johns Hopkins University, Baltimore, vol. ii.

the Biological Laboratory of the Johns Hopkins University, however, has demonstrated that the increased respiration of an animal exposed to heat is due to two causes, warmed blood and stimulation of the skin by the heat, and that probaby skin stimulation is the more important factor. Some of Sihler's criticisms of Goldstein's experiments have been met by Gad and von Mertschinsky,[1] who have made it evident that increased temperature of the blood stimulates the respiratory centres, or increases their irritability. Section of the vagi does not check heat dyspnœa, so that this does not result primarily from the action of the increased temperature upon the terminal pulmonary expansion of these nerves. The removal of afferent impulses from the skin by section of the spinal cord does, however, exert so marked an influence that it cannot be doubted that heat stimulation of the skin is an important element in the causation. I have convinced myself of the correctness of Sihler's explanation by observing that in the hot box at temperatures of 90°–95° F. (32.2°–35° C.) rabbits often preserve their normal temperature, and still their breathing is markedly increased, and that, on the other hand, upon taking them out of the box the respirations may sink before the internal temperature begins to fall. In one striking experiment the respirations fell immediately to about normal upon removing from the hot box a rabbit whose skull had been trephined on each side of the median line, and the optic thalami punctured with a needle.

We cannot transfer directly to human beings the results of experiments on heat dyspnœa in animals, because in the latter respiration has a far more important function in temperature regulation than in the former. To keep cool a dog pants under circumstances when a man sweats. As heat regulation is largely influenced by the cutaneous temperature, it is not improbable that in man

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[1] Gad and v. Mertschinsky: Virchow u. Hirsch's Jahresbericht, 1881, Bd. i. S. 197.

heat stimulation of the skin is less prominent than the warmed blood acting upon the respiratory centres in increasing the frequency of respiration in fever.

Inasmuch as disturbances of the heart and of the circulation in general are among the most important symptoms of fever it is natural that much attention should have been given to the study of the effects of heat upon the organs of circulation. The supposed injurious effects of prolonged high temperatures in fever have been usually attributed especially to some toxic action of heat upon the heart.

That the pulse-rate is quickened by artificially heating rabbits and dogs has long been known. The positive demonstration that this acceleration is due to the direct action of the heated blood upon the mammalian heart itself was first given by my colleague, Prof. Martin.[1] By conducting through the dog's heart, isolated physiologically by the ingenious method which he devised, Martin proved that the heart "beats quicker when supplied with warm blood and slower when cold blood is supplied to it; also, that the rate of beat depends much more upon the temperature of the blood in the coronary arteries than on its temperature in the right auricle or ventricle." These experiments make it unnecessary to recur to any action of the heated blood upon extrinsic cardiac nerves or nerve centres in order to explain the quickened pulse of fever. Moreover, Fick[2] found that the nervous centres of the heart and bloodvessels are unaffected by heating the blood flowing through the carotid arteries in the manner adopted by Goldstein in his experiments on heat dyspnœa.

Prof. Martin has kindly permitted me in this connection to mention certain unpublished results of experi-

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[1] Martin: The Direct Influence of Gradual Variations of Temperature upon the Rate of Beat of the Dog's Heart, Philosophical Transactions of Royal Society, part ii. 1883.

[2] Fick: Pflüger's Archiv, Bd. v.

ments which he is now conducting upon the effects of heat and cold on the isolated heart. As these results are pertinent to our subject I gladly avail myself of this privilege. The table of an experiment which I have examined shows that the isolated cat's heart beats regularly and more and more rapidly as the temperature of the blood is gradually raised to 111.2° F. (44° C.). At this point the beats become irregular, but are restored to their normal rhythm by feeding the heart with cooler blood. The temperature of about 111° F. (43.9° C.) appears to be a critical one for the isolated heart. Above 111.2° (44° C.) to 113° (45° C.) the pulsations become slower instead of quicker as the temperature is raised. At 122° F. (50° C.) the heart's action ceased, but the heart was made to beat again by supplying it with cooler blood, showing that the cessation was not due to heat rigor. This interesting experiment teaches among other things that very high temperatures may produce results differing not only in degree but also in kind from those of temperatures only a degree or two lower.

We may consider it then established that increased frequency of the pulse in fever is referable to the direct action of the warmer blood on the nervo-muscular substance of the heart itself. Clinical observation of cases of fever makes it evident that there may be and often are present other circumstances which influence the rapidity of the heart's pulsations, circumstances which in themselves may slow or may quicken the p ulse Large series of statistics, therefore, are required to bring out the ratio between the pulse-rate and the temperature in fever and even then for any given temperature the maximum and the minimum pulse-rates lie so far apart that the statement of the average increase in the frequency of the pulse for each degree of rise of temperature, such as has been computed by Liebermeister, has very little value.

Not only is the pulse-rate quickened in fever, but there.

are often other and more serious circulatory disturbances. In the fever produced in rabbits by injection of the swine plague bacillus I find a reduction of the blood-pressure measured in the carotid artery, and others have obtained similar results in the artificial fevers of animals. The determination of the blood-pressure in fevers of human beings by means of Basch's sphygmomanometer has given, in the hands of different experimenters[1] such contradictory results, that no conclusion can be drawn, unless it be the very probable one that the blood-pressure varies, being sometimes high, sometimes low, and sometimes normal in fever. That the arterial tension is often reduced is made evident by the marked dicrotism of the pulse wave. This dicrotism, however, characterizes particularly septic and typhoid types of fever and is absent during the chill of intermittent fever and often in exanthematous and some other fevers, so that we cannot consider the blood-pressure and arterial tension as having any such definite relation to fever as does the pulse-rate.

It has been observed by Paschutin, Senator, and Mendelson,[2] that the blood pressure rises with increasing bodily temperature, produced by exposure to heat. Mendelson found that the pressure begins to sink as the temperature approaches a point incompatible with life. In these experiments the animals were subjected to rapid elevations of temperature. I find that when a rabbit is gradually and cautiously heated in the hot box used in my experiments, the rise of temperature is less marked, and may not surpass even for temperatures of 107° F. (41.7° C.), the normal limits of variation which may be found in the blood-pressure of the same animal examined at different times. These measurements, however, are

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[1] Von Basch, Zadek, Arnheim, Wetzel.

[2] Paschutin, Ludwig's Arbeiten, 1873. Senator, DuBois-Reymond's Archiv, 1883, Supplement-Band. Mendelson, On the Renal Circulation during Fever, Amer. Journ. Medical Sciences, October, 1883.

not very conclusive, for, as has been already remarked, rabbits which have been operated upon do not stand well artificial heating.

I have observed that the rhythmical contractions of the bloodvessels of the rabbit's ear are feeble or absent when the temperature is much elevated by artificial heating; whereas, it will be remembered that in experimental septic fever these contractions are irregular and exaggerated.

Upon the whole, I think that we are justified in concluding that the variations of arterial tension in fevers are much less dependent upon increased temperature than upon other factors, such as infection.

But the corner-stone of the doctrine which teaches that a chief source of danger in fevers is the elevation of temperature, is not the effect of increased temperature upon the pulse-rate or the arterial pressure, but it is the belief that prolonged high temperature exerts a directly paralyzing influence upon the heart. The main support of this belief is not the admitted fact that extremely high temperatures paralyze the heart, for these critical temperatures lie far above the ordinary high temperatures of fever, and in a region where all admit the dangers of the excessive internal heat. The stately superstructure has been built up chiefly on the basis of experiments showing that when the internal temperature of animals has been maintained for some time at a high point by exposure to external heat, parenchymatous or fatty degeneration of the heart muscle ensues. It is true that all experiments are not in accord upon this point, and that, as a rule, pathological anatomists have not given adherence to the doctrine that parenchymatous degenerations are chiefly dependent upon high temperature, still this doctrine has gained a wide acceptance among clinical men, and is advocated with especial force by Liebermeister. I have, therefore, thought it desirable in my experiments to give especial attention to this question.

Among previous experimenters on artificial heating of animals, Iwaschkewitsch, Wickham Legg, and Litten may be mentioned as finding parenchymatous or fatty degeneration of the heart, liver, and kidneys; and Walther, Obernier, and Naunyn as obtaining only negative results.

It is not necessary here to enter into a criticism of these different experiments, which are of very unequal value. Litten's[1] experiments on the one side, and Naunyn's[2] on the other, appear to be the most carefully conducted. Litten, whose experiments are those usually cited, kept guinea-pigs in a double-walled metallic box which was at a constant temperature of 98.8° F. (37° C.) with dry air, or of 96.6° F. (36° C.) with moist air. He never failed to find fatty degeneration at the end of thirty-six to forty-eight hours. The liver was first affected, and then the heart and kidneys, which become fatty by the second or third day. The animals did not survive longer than five or six days, and by that time the fatty degenerations had reached an extreme degree. Von Recklinghausen[3] urges with apparent justice against these experiments that the enforced inactivity of the muscles and the imperfect ventilation may have had as much to do in causing the degenerations as had the high temperature. These objections find support in the experiments of Naunyn, who, making use of a much larger and better ventilated heating box than Litten, failed to find any parenchymatous or fatty degeneration in his rabbits after they had been exposed for two weeks to higher temperatures than Litten employed.

As my experiments confirmed in other respects Naunyn's results, I was quite unprepared to find that my rabbits, after a variable period of artificial heating quite

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[1] Litten, Virchow's Archiv, Bd. 70. [2] Naunyn, op. cit.

[3] Von Recklinghausen: Handb. d. Allg. Pathologie d. Kreislause u. d. Ernährung, p. 512, Stuttgart, 1883.

constantly presented fatty degeneration of the heart, liver, and kidneys, and sometimes of the diaphragmatic and intercostal muscles. I never found the degeneration at so early a period as did Litten. It was not until the rabbit had been kept for at least a week with an average rectal temperature of 106° F. (41.1° C.) that the degeneration was noticed, and then only in moderate degree. The higher and the less fluctuating the internal temperature, the more certain was the degeneration to appear. I could reckon upon obtaining rabbits with well-marked fatty degeneration of the heart, by keeping them for ten days with a rectal temperature between 107° F. (41.7° C.) and 108° F. (42.2° C.). I am not prepared to account for the discrepancy in this respect between Naunyn's and my experiments. The box used was larger than that employed by him, and every care was taken to keep it well ventilated by leaving at least one-third and often one-half of the top open.

I do not think that my experiments altogether do away with the force of von Recklinghausen's criticisms. The fact that in these experiments the degeneration made its appearance at the end of a week or ten days, and in Litten's in forty-eight hours, to say nothing of Wickham Legg finding it at the end of twelve hours, would suggest that if the rabbits were heated in a still larger and better ventilated apartment, the degeneration might not occur at all, or might be deferred to a much later period. In my opinion, however, even if full allowance be made for this line of argument, we must still admit that prolonged high temperature is a factor in the causation of fatty degeneration.

That it is not the sole factor no one can doubt. As is well known, fatty degeneration is produced by anæmia and by a variety of poisons, and even in fevers most pathologists are convinced that it bears a closer relation to the kind and the degree of infection than it does to the height of the temperature. It is more frequently

absent than present in pneumonia, even where there have been symptoms of heart failure.

The kind of degeneration present in my rabbits was fatty and not parenchymatous. Probably all who make many post-mortem examinations will agree with von Recklinghausen, that altogether too liberal use has been made of the diagnosis of parenchymatous degeneration, and not sufficient account has been taken of the anatomical changes of the parenchyma produced by post-mortem chemical changes, such as acid formation, etc.

In order to determine what influence is exerted by infection combined with high temperature, I inoculated a rabbit, which had been in the hot box for four days, with the bacilli of swine plague. These bacilli, if not identical with, are closely allied to those of rabbit septicæmia, and are extremely virulent for rabbits. In thirty-six hours the animal, which had remained at a high temperature in the box, was dead, with characteristic lesions of the disease, and the most extreme fatty degeneration of the heart and other organs was found. As in other experiments the degeneration had not made its appearance at this early date, there can be no doubt that the infection was an important element in the causation. That it received powerful support in the high temperature, however, is proven by the fact that little or no degeneration of the heart is observed after infection with this organism when the animal is kept at ordinary temperatures.

Admitting, then, that high temperature aids in the causation of fatty degeneration of the heart in fever, the question arises, What do we know of the effects of this degeneration upon the functions of the heart? I will say nothing of the growing tendency to transfer a large part of the classical symptomatology of Quain's fatty heart to other conditions, particularly to disease of the coronary arteries and chronic myocarditis; we are concerned at present only with the occurrence of this degeneration in fever. Have we not been somewhat hasty in assigning

to degenerations of the heart's muscle so large a share in the production of heart failure in fevers? One cannot look at a muscular fibre in which the striated substance is all replaced by fatty globules, and suppose that its functional activity was unimpaired; but into what serious errors should we fall if we attempted to deduce from the anatomical changes in the liver cells or the renal epithelium the corresponding functional disturbances? Certain it is that symptoms which are usually considered those of heart failure are often enough present in fevers without finding at the autopsy any degeneration of the heart; and, on the other hand, such degeneration may be discovered without any history of these symptoms, although, of course, the two are often associated.

In the face of these doubts it seemed desirable to determine, if possible, experimentally the damage inflicted upon the cardiac functions by the presence of fatty degeneration of the heart muscle. That this degeneration may exist without apparent injury is rendered probable by the fact that a rabbit which has been kept for three weeks in the hot box at a high temperature, and in which there is every reason to suppose that fatty degeneration has occurred, may present no symptoms of heart paralysis, and when removed from the box appear and remain perfectly normal. An instance has already been mentioned where one rabbit at the end of three weeks was killed and presented marked fatty degeneration of the heart; and another, which had possessed a higher average rectal temperature, was removed from the box at the end of the same period, and appeared for ten days perfectly normal, when it was used for another purpose. That this degeneration can be recovered from is, moreover, rendered probable by clinical experience, and is universally admitted.

Once in teasing out, in a warm room, a bit of fatty heart muscle from one of the rabbits, I made a curious observation. Near the edge of the cover glass, where there

was a slight current in the physiological salt solution, rhythmical contraction was observed in a group of muscle-fibres. This interesting spectacle could be watched under the microscope for ten minutes. These contracting fibres were filled with fatty globules, and only here and there, and then indistinctly, could any trace of striation be detected. This observation teaches that a fatty degenerated muscular fibre is capable of contraction, but, of course, warrants no further conclusions.

Far more important than any inferences which can be drawn from such observations is the measurement of the actual blood-pressure in animals whose hearts have undergone fatty degeneration. This I have done in three instances. The rabbit was removed from the box at the end of ten days to two weeks, and the pressure in the carotid artery was measured by a mercury manometer attached to Ludwig's kymograph. In no instance was the blood-pressure found to be lower than that normally present in rabbits. In an experiment recently performed, the average pressure was 125 mm. of mercury; the pulsations were regular; the heart responded to stimulation of the vagi in an entirely normal manner. After such stimulation the pressure in one case rose to 176 mm. of mercury. Immediately after the measurement of the blood-pressure the rabbit, as in the previous instances, was killed, and marked fatty degeneration of the muscular fibres was found. In many of the fibres the striation could not be made out, and only fatty globules were visible; in others, which also contained fatty granules, the striation was distinct. The degeneration involved the whole muscular substance of the heart. A similar appearance in a human heart would be considered to indicate well-marked fatty degeneration.

These experiments show that a rabbit's heart which has undergone marked fatty degeneration from exposure to heat, may perform its functions, to all appearances, and for the time being, in a perfectly normal manner.

There is at least one consideration which should make us cautious in drawing far-reaching conclusions from these experiments. There are diseases of the heart—I need only refer to lesions of the coronary arteries—in which the functions of the organ are performed for a longer or shorter time, apparently in a perfectly normal way, and then heart failure suddenly appears. It is probable that here too the blood pressure would be found normal at a certain period of the disease, and still it would be an error to suppose that the lesion does not damage the heart.

Whatever force there may be in this analogy, I still think that these experiments, as well as careful pathological and clinical observations, necessitate some revision of the current opinions concerning the significance of fatty degeneration of the heart in fever.

So much time has been devoted to a consideration of the effects of heat upon the respiration and the heart that the limits of the present lecture will permit hardly more than a summary of the effects exerted by heat upon other functions and organs of the body. On account of the great clinical importance of the subject it seemed desirable to treat with especial fulness the influence of increased temperature on the heart.

What part has increased temperature in producing febrile consumption of tissue? In the first lecture mention was made of Pflüger's experiments showing that animals with elevated temperature, produced by exposure to heat, absorb more oxygen and excrete more carbonic acid than at the normal temperature. This is in conformity with the general law that within certain limits cell activity is more energetic at high than at low temperatures. It was also shown in the first lecture that only a comparatively small part of the increased oxygen absorption and carbonic acid elimination in fever can be referred to the immediate effects of high temperature. It has not been demonstrated that the respiratory gases in

human beings are increased by artificial elevation of temperature. Indeed, Voit[1] was unable to find any such effect of increased temperature in human beings on the respiratory gases as both he and Pflüger observed in animals.

Inasmuch as increased disintegration of nitrogenous material is such a prominent disorder in fever, much attention has naturally been given to determining how far this can be explained by elevated temperature. That it cannot all be so explained is proven by the interesting observation of Sydney Ringer, that excessive elimination of urea antedates the rise of temperature in intermittent fever, and Naunyn has found the same to be true of the septic fever of dogs. The experiments which have been made to determine the influence of artificial heating on the amount of urea excreted by man and by animals have yielded contradictory results. A number of these experiments are of little or no value, because no attention was given to establishing beforehand nitrogen equilibrium. Schleich's[2] experiments may be mentioned as, perhaps, the most accurate of those showing an increase in the urea excreted under the influence of exposure to heat. The more recent experiments of Simanowsky[3] were made in Voit's laboratory upon a dog with especial precautions as to the establishment of nitrogen equilibrium. He failed to find any increase in the excretion of urea as the result of exposure to external heat. While then this question must be left at present *sub judice*, there can be no doubt that only a part at least of the excessive disintegration of nitrogenous substance in fever can be assigned to the influence of the increased temperature.

The loss of weight exhibited by animals kept for a long time in a hot atmosphere is usually explained by the excessive evaporation of water from the body. In

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[1] Voit: Zeitschrift für Biologie, Bd. xiv.
[2] Schleich: Arch. f. exp. Path. u. Pharm., Bd. iv.
[3] Simanowsky: Zeitschr. f. Biologie, Bd. 21.

many of my experiments the rabbits were freely supplied with food and water, and still the loss of weight was very noticeable. I am inclined, therefore, to attribute to the increased temperature under these conditions a decided influence upon the consumption of tissue.

Senator[1] found the urine of rabbits artificially heated to contain more albumen than is ever found in the urine of healthy rabbits. This observation I have not been able to confirm on the rabbits in my experiments, and probably this difference is to be explained by the more rapid and intense heating employed in Senator's experiments. Senator explains the heat albuminuria by the rise of arterial pressure in the renal vessels, but this is not in conformity with the interesting experiments of Mendelson,[2] who found by means of Roy's oncometer that both in thermic and in septic fevers of dogs the kidney is anæmic, while the general blood-pressure is elevated.

No satisfactory explanation has yet been offered of the diminution of perspiration which distinguishes fever so strikingly from the condition produced by exposure to high external temperatures. Luchsinger's assertion that this is the result of lessened irritability of the sweat centres in the spinal cord remains to be proven, and at the best is not a satisfying explanation.

Bokai,[3] in a recent experimental research on intestinal peristalsis in thermic and in septic fevers, comes to the conclusion that the constipation of fever is to be explained by the heated blood stimulating the nerves inhibiting intestinal peristalsis. If this should be confirmed, then it would be proven that at least three symptoms of fever,

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1 Senator: Du Bois-Reymond's Archiv, 1883, Supplement-Band.

2 Mendelson: Op. cit.

3 Bokai: Archiv f. exp. Path. u. Pharm., Bd. 23.

the quickened respiration and pulse and the constipation, are direct effects of elevated temperature.

When we consider the important nutritive changes in the muscles accompanying increased thermogenesis, we shall be inclined to attribute in part, at least, to these alterations and the associated abnormal innervation, rather than to increased temperature, the muscular pains and weakness which form such an early and frequent complaint in many fevers.

The investigations hitherto published of changes in the blood produced by increased temperature within febrile limits are not of sufficiently definite and satisfactory nature to warrant any consideration on the present occasion.

Nor am I acquainted with any experimental evidence (save Bokai's work already mentioned) that increased temperature is concerned in the production of the digestive disorders of fever. It has already been said that the rabbits with high internal temperatures in the hot box ate greedily, but these voracious animals cannot be considered favorable subjects to test this question.

Especial emphasis has been laid by Liebermeister and those who accept his teachings upon the dependence of the nervous symptoms of fever, particularly the so-called typhoid symptoms, on the elevation of temperature. There is, however, abundant clinical evidence to disprove this doctrine. Reference need be made only to relapsing fever, and especially to the aseptic fever described by Genzmer and Volkmann, in which there is entire absence of the whole group of so-called nervous symptoms. Moreover, Liebermeister's opinion in this respect is not supported by adequate experimental evidence. Unless the temperature of the brain or of the entire animal be brusquely raised to a high point by coarse methods, no disturbance of the cerebral functions is noticed until the temperature reaches a critical point, beyond which further increase is likely to prove rapidly fatal. At this critical

point the animal, which before has lain quietly, becomes very uneasy, and if the temperature rise higher it has convulsions and coma and dies.

I have endeavored to bring before you in this lecture the experimental evidence relating to the effects of increased temperature upon the general condition of the body and upon the functions of its various organs. I have given account, as briefly as possible, of some experiments which perhaps shed additional light upon this important subject. In the course of this lecture emphasis has repeatedly been laid upon the necessity of controlling the results of the experimental method by clinical observation, and here and there I have endeavored to institute this control. Further than this I shall not attempt to set before you the clinical evidence regarding the effects of increased temperature in fever. There are those here more competent than I to deal with this side of the question. We may feel assured that when all the facts are before us and are properly interpreted, there can be no lack of harmony between the results of experimental and those of clinical investigations.

LECTURE III.

THE ETIOLOGY OF FEVER.

We considered in the last lecture the experimental evidence concerning the effects of increased bodily temperature. An advantage of the experimental over the clinical method of investigating this subject is that it enables us to study the effects of heat upon the whole body and its various functions without the intervention of disturbing factors, such as infection, which complicate the clinical analysis of febrile phenomena with reference to this question.

We found that animals may be kept at high febrile temperatures for at least three weeks without manifesting any serious symptoms. The only functional disturbances which could be attributed directly to the influence of the elevated temperature were increased frequency of respiration and quickened pulse. The rapid respiration was found to be due partly to stimulation of the skin by external heat and by the warmed blood, and partly to the action of the warmed blood on the respiratory centres. The quickened pulse could be positively referred to the effect of the warmer blood upon the heart itself. No definite relation could be established between the variations of arterial tension which occur in fever and the height of the temperature.

Although the experiments narrated showed that prolonged high temperature is an element in the causation

of fatty degeneration of the heart, they also indicated that other factors, such as infection, are concerned in the production of this lesion. Moreover, experimental evidence was found in support of clinical facts showing that this alteration may exist without serious interference with the functions of the heart, so that the conclusion seems justified that failure of the heart's power in fever is less an effect of high temperature than of other concomitant conditions.

Of the other disturbances in fever we learned that the increased consumption of tissue can be explained only in relatively small part by the elevation of temperature. The lessened perspiration, the renal disorders, and the digestive disturbances (with the possible exception of constipation) are referable also chiefly to other causes than the increased temperature. Both experimental and clinical observations strongly support the view now widely accepted that the disturbances of the sensorium which constitute so prominent a part of the group of so-called typhoid symptoms, are dependent in far higher degree upon infection or intoxication than upon the heightened temperature.

Although no attempt was made to analyze in detail the clinical evidence relating to the effects of high temperature, attention was called to the fact that the absence of all serious symptoms in many cases of relapsing fever, and in the so-called aseptic fevers in spite of prolonged high temperatures, strongly support the conclusions derived from the experimental study of the effects of heat upon man and animals. Even in fevers, such as typhoid fever and pneumonia, where the height of the temperature is undoubtedly a most important index of the severity of the disease, there exists no such parallelism between the temperature and the nature and the severity of the other symptoms as we should expect if these symptoms were caused by the increased heat of the body.

It was emphasized that the results of experimental investigations should not be permitted to control the treatment of fevers, more particularly the use of so-called antipyretic agents. These agents, whether hydrotherapeutic or medicinal, influence, as is well known, many functions besides reducing the temperature. I need only refer to the powerful influence of cold baths upon the circulation and the nervous system, and to the action of antipyrin and other antithermic drugs upon the nervous system.

Reasons were given for assigning to hyperpyrexia and insolation a position separate from other febrile conditions in the discussion as to the effects of elevated temperature.

Before leaving this subject of the effects of increased temperature, I wish to call attention to one consideration which should perhaps influence our opinion on this much disputed question. Is it a matter of indifference, so far as the effects of febrile temperatures are concerned, in what manner the increase of temperature is brought about? We have seen that heat regulation, heat production, and heat loss are disturbed in fever; but, as experience shows, not always in the same manner or the same degree. In one case the incoördination of the regulating mechanism may be most apparent, the temperature fluctuating strangely up and down; in another case the heat-producing processes are excited to the utmost; and in another the circulatory changes in the skin, the vasomotor disturbances, are the most prominent phenomena. Now this varying interplay of the factors which cause febrile rise of temperature doubtless corresponds to varying conditions of innervation, of structure and of function of certain tissues of the body. May we not reasonably suppose that these varying conditions of the tissues directly associated with the rise of temperature may influence their tolerance of increased body heat? We have not the experimental or the clinical data which would

enable us to give a definite answer to the question here propounded, and it would lead me too far from the theme of the present lecture to attempt to sift the equivocal evidence which might be gathered. I suggest this question, however, as one worthy of more attention than it has hitherto received.

I wish now to invite your attention to some considerations concerning the etiology of fever. In this era, when etiological studies occupy the foremost rank in medical science, it will naturally be expected that a discussion of the general pathology of fever, even though it does not aim at completeness, will not leave wholly untouched the etiological aspect of the subject.

The general etiology of fever relates mainly to a consideration of the agents producing fever, the so-called pyrogenic substances. It is, moreover, only certain general characters of these agents which can be properly considered here. Most of the questions which at present engage so prominently the attention of physicians concerning the specific causes of individual fevers belong, of course, to the special etiology of fevers, and therefore do not lie within the limits of our subject. But even with these limitations we cannot in treating of the general etiology of fever consider the febrile processes so much in the abstract as we have done hitherto. We must come into closer contact with the individual forms of fever.

At the start it should be said that probably in no instance are we acquainted with the actual substance or substances upon which the febrile disorder of animal heat immediately and directly depends. We deal here, as elsewhere in medicine, not with direct but with remote causes. But in no department of etiology have we advanced nearer the proximate causes than in many of the infectious fevers. To be convinced of the immense progress which has been brought about by the etiological study of fevers, let one glance over some of the

older books on fevers, such as Percy's or Selle's,[1] with their endless divisions into symptomatic genera and species, and their barren speculations. Percy, for instance, describes no less than one hundred and fifteen different kinds of fever.

In all ages it has been customary to divide fevers into two great groups, viz.: those which are secondary to some local cause, usually an inflammation, and those which cannot be explained by the presence of any local lesion. The explanation of the symptomatic seemed so much clearer than that of the essential fevers that attempts have repeatedly been made to place all fevers in the symptomatic group. It is a curious fact that the two methods which have been of the greatest service in the study of fevers, each, when first introduced, led to an entire misconception of the nature of fever. Boerhaave, who was the first to make any extensive use of the thermometer at the bedside, supposed that this instrument indicated a reduction of the bodily temperature during the febrile chill. He therefore taught that increased frequency of the pulse and not the elevation of temperature is the constant and essential symptom of fever. If we except de Haen's correction, which never became widely known, it was not until the middle of the present century that Boerhaave's error was overthrown. A no less serious misconception sprang from the study of the pathological anatomy of fevers in France during the early part of the present century. The exaggerated ideas of the immediate followers of Bichat as to what can be accomplished by pathological anatomy led them to the belief, for a long time widely accepted, that there is no such thing as an essential fever, that all fevers are symptomatic of some local disease. This error of Brous-

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[1] Percy: Die gesammte Fieberlehre, Pesth, 1820. The original is in French.

Selle: Rudimenta Pyretologiæ Methodicæ, Berolini, 1773.

sais, one of the most influential and eloquent medical teachers of this century, is plainly traceable partly to the fact that his autopsies were chiefly of typhoid fever, and partly to the belief that the lesions found at the autopsy suffice to explain all of the manifestations of the disease during life. But we need not stop to trace the fate of the various attempts to overthrow the doctrine of essential fevers. I have mentioned one attempt chiefly on account of the suggestive lessons it conveys rather than from a desire to enter into historical details which I have hitherto purposely avoided.

The division of fevers into symptomatic and essential fevers is one of undoubted practical utility, and is not likely to be abandoned. But it cannot truthfully be said that this popular classification has been of much assistance in advancing our knowledge. Close inspection shows that the boundary lines between the two groups of fevers are vague and shadowy. Probably no one any longer believes that traumatic fever, the principal type of the symptomatic group, is due to increased production of heat in the seat of inflammation, which, acting like a furnace, was once thought to warm the whole organism, or to the irritation of nerves connected with the inflamed region. The opinion of Billroth and of Weber is now generally accepted, that traumatic fevers are caused by the absorption of pyrogenic substances from the inflamed district. Symptomatic fevers as well as essential fevers, therefore, are dependent upon the presence within the blood of fever-producing agents. Many essential fevers, moreover, resemble the symptomatic ones in the existence of inflammation, or necrosis at the portal where there is reason to believe that the pyrogenic agents gain access to the general circulation. A distinction in these cases cannot be based on the ground that in symptomatic fevers only chemical substances, although possibly the products of bacteria, enter the circulation, and in essential fevers microörganisms invade the blood, for

such a distinction would place cholera and possibly tetanus and typhoid fever among the symptomatic fevers. These considerations show how vague and unsatisfactory are the distinctions between symptomatic and essential fevers. Still, similar criticisms can be made of many of our artificial classifications which nature is under no compact to observe, and we should undoubtedly be put to great inconvenience if we attempted to dispense with the epithets symptomatic and essential as applicable to different forms of fever. There are, however, other points of view which seem to me more fruitful in the study of the etiology of fever than those embodied in these distinctions. I refer to the differences in the nature of fever-producing agents, concerning which our knowledge, although still very imperfect, has been materially increased within recent years. And here again we are greatly indebted to the results of experiments upon animals.

Much light has been shed upon the causes of a certain class of fevers by a series of experiments, which received their impulse from the important studies of Alexander Schmidt and his pupils upon the physiology of the blood. A particular direction was given to these experiments by the often repeated observation that fever and other injurious effects may follow the transfusion of blood, especially when the blood of one species of animal is transfused into an animal of another species. In order to test the supposition that these bad symptoms are due to an excess of fibrin ferment Köhler[1] injected into the vessels of animals blood made rich in fibrin ferment and fibrino-plastic substance, and found that this blood when injected in large amount into the jugular vein causes sudden death by rapid coagulation of the blood in the right heart and pulmonary arteries, but when injected in

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1 Köhler: Ueber Thrombose und Transfusion, u. s. w. Inaug. Diss., Dorpat, 1877.

smaller amount or in a different manner produces a typical febrile attack bearing a close resemblance to that following the injection of putrid fluids. Angerer[1] then found that a similar fever, although less intense and more gradual in its development, may be produced by the injection of blood into the peritoneal cavity or the subcutaneous tissue, or even by an extravasation of blood. Although in these experiments it was believed that fibrin ferment is the pyrogenic agent, Edelberg[2] was the first to produce fever and other symptoms of intoxication by the injection of this ferment isolated according to Schmidt's method.

In the light of these experiments it was to be expected that other ferments would be examined with reference to their pyrogenic power. Schmiedeberg[3] discovered that injections of histozyme into the blood of dogs produced high fever associated with general illness, and particularly with diarrhœa. The ferment to which Schmiedeberg has given the name histozyme he believes to be present normally in small amount in the body, and to be concerned in the dissociation of the nitrogenous constituents of the tissues. He concludes from his experiments that an excessive accumulation in the body of this normal ferment gives rise to fever with increased metamorphosis of nitrogenous materials. Schmiedeberg thinks it probable that the fibrin-ferment solutions employed by Edelberg in his experiments contained also histozyme, and that the pyrexia was due to the latter substance.

Following these observations concerning the pyrogenic power of fibrin-ferment and histozyme comes the discovery of von Bergmann and Angerer[4] that injection of

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[1] Angerer: Klin. u. Exp. Untersuch. üb. d. Resorption v. Blutextravasate, Würzburg, 1879.

[2] Edelberg: Arch. f. exp. Path. u. Pharm., Bd. xii.

[3] Schmiedeberg: Ibid., Bd. xiv.

[4] Von Bergmann u. Angerer: D. Verhältniss d. Fermentintoxication. Festschrift, Würburger Universität, 1882, i. 135.

pepsin and of trypsin into the blood of dogs causes a well-marked fever with characters like those of the other ferment intoxications described. A valuable calorimetrical study of pepsin and trypsin fevers has been made by Wood, Reichert, and Hare.[1] These authors, as well as Ott,[2] have demonstrated that it is not the pepsin and the trypsin ferments themselves which constitute the pyrogenic agents, but some contaminating substance, which seems to be a peptone. That peptones artificially prepared contain poisonous principles has been known for some time, and Brieger[3] has succeeded in isolating a crystallizable poisonous ptomaine, called pepto-toxin, from commercial peptone and from that formed by the artificial digestion of fibrin. This ptomaine, however, is not identical with the pyrogenic agent found by Ott and by Wood and his colleagues in commercial pepsin. To this list of pyrogenic substances obtained from impure ferments may be added leucin, and, according to Ott, papayotin and neurin which produce marked fever when injected into the blood in small quantity. The substance sold under the name of papoid possesses marked pyrogenic power when its filtered aqueous solution is injected into the blood. This substance contains principles belonging to the peptone or albumose group. Dr. Mall, Fellow in Pathology at the Johns Hopkins University, has isolated from commercial papoid a bacillus, which in pure cultures exerts a powerful peptonizing action on fibrin and on connective and elastic tissues. The bacillus itself is not pathogenic, but an albumose or some similar substance produced by its activity, has pyrogenic power when injected into the blood.

It does not appear that any one has actually isolated the pyrexial agent from the various ferments employed in these experiments. Certainly no such agent has been

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[1] Wood, Reichert, and Hare: Therapeutic Gazette, 1886.

[2] Ott: Journal of Physiology, vol. viii.

[3] Brieger: Ueber Ptomaine, Berlin, 1885.

obtained in a crystalline form, which is the test of its purity, if we except Brieger's pepto-toxin, the pyrogenic capacity of which has not been established. It has been alleged that the fever-producing agent is the same in all these ferment intoxications, but this has not been proven nor does it seem probable.

On better grounds it has been urged by von Bergmann and Angerer, that all of the substances in the group of pyrexial agents now under consideration, cause fever by producing the same change in the blood. These authors claim that this change is the formation in the circulating blood of an excessive amount of fibrin ferment, which leads either to coagulation or to stasis in the capillaries, particularly those of the lungs and of the intestines. One of the main arguments for this view is the fall of blood pressure which von Bergmann and Angerer observed after injections of pepsin and of pancreatin, but this fall can be explained in other ways than by supposing that the pulmonary capillaries are occluded, and, moreover, Wood, Reichert, and Hare find that the blood pressure often rises in the course of pepsin fever. It does not seem to me that we are any more able to explain in exactly what manner the pyrogenic substances act in this class of fevers than in other fevers. The idea, however, that the liberation of fibrin ferment in abnormal quantity is capable of causing fever, finds support not only in experiments which have been mentioned, but also in the fact that injections of hæmoglobin solutions, and of large quantities of water into the blood, produce fever.

But you, perhaps, by this time have asked yourselves what bearing all of these experiments with various pyrogenic substances have upon the etiology of human fevers. They have, in my judgment, an important bearing on this subject. However obscure may be the explanation of the mode of action of these substances, however doubtful may be their exact chemical composition, they have certain common characteristics which are calculated

to shed light upon the causation of some obscure febrile disorders of human beings. In the first place, the members of this group of pyrogenic substances, if not identical with certain physiological ferments, are readily produced by them, quite independently of the action of bacteria or other microörganisms. In the second place, some of these substances are present normally in small amount in the body, and if their elimination is impeded, or their formation is excessive, there is reason to believe that they become efficient causes of fever. In the third place, these pyrogenic substances may be produced, again without the action of bacteria, in extravasated blood, or by the abnormal disintegration of tissues, and if they are absorbed from these sources in such a condition, or in so large an amount that nature cannot render them harmless, they are capable of producing fever. It is customary to call the morbid condition produced by the absorption of these substances, ferment intoxication in analogy with the term putrid intoxication, applied to the diseases caused by the absorption of the products of putrefactive bacteria. The term ferment intoxication seems to me to imply more than our knowledge warrants, but it is not of much use to contend against names which have gained currency. It is probable that some of the pyrogenic agents in this group belong to the class of leucomaines, but our present information regarding these bodies does not justify any positive statements on this point.

Although the etiology of individual fevers does not belong to our subject, I cannot forbear calling your attention to certain febrile conditions which seem to be produced by the accumulation of substances that are either normal constituents of the body or are the result of chemical processes, differing but little from physiological ones.

To this category probably belongs the so-called aseptic fever, first described by Genzmer and Volkmann.[1] These

[1] Genzmer and Volkmann: Volkmann's Sammlung, No. 121.

surgeons have established the fact that there are traumatic fevers not caused by the absorption of septic material, and that severe injuries and wounds which pursue an entirely aseptic course, are not infrequently associated with considerable elevation of temperature. This aseptic fever is usually to be observed with extensive wounds or injuries in which there is much lacerated tissue or extravasated blood to be disintegrated and absorbed. It occurs not only with wounds correctly treated by antiseptic methods, but also with subcutaneous injuries, particularly fractures of the large bones, where there can be no suspicion of the action of bacteria. Aseptic traumatic fever differs by such marked characteristics from septic fever, that there can be no doubt that the two types of fever are etiologically distinct. Aseptic fever has no prognostic significance; its only symptoms are the elevation of the temperature, which may mount to 104° (40° C.), or even 105.8° (41° C.), and the increased frequency of the pulse. The entire absence of all the intoxication symptoms of septic and infectious fevers, such as the benumbed sensorium, the dry tongue and skin, the lessened secretion of urine, I have already referred to in confirmation of the belief that these symptoms are not dependent upon the rise of temperature. Genzmer and Volkmann assign as the cause of aseptic traumatic fever, the absorption of substances resulting from the disintegration of the wounded tissues and of the extravasated blood, and state that these substances probably do not differ markedly from those produced by physiological tissue metamorphosis. This explanation certainly has received decided support by the experiments which I have described in this lecture, a large part of which have been performed since the publication of Genzmer and Volkmann's article. It has been suggested that aseptic traumatic fever is a reflex neurosis, and this suggestion cannot be absolutely rejected as a possible explanation, but for various reasons,

which cannot here receive further consideration, the usually accepted explanation is the more probable one.

An instructive case of ferment intoxication has been reported by Cramer.[1] There existed in a young woman a cyst, the size of a goose's egg, between the fibres of the semitendinosus muscle. The cyst was developed from a cavernous angioma, and was filled with dark fluid blood. The patient had had fever for almost two years up to the day of the operation. The cause of the fever could not be discovered. Immediately after the removal of the cyst the fever stopped and did not return. In this case the cavernous structure of the cyst wall accounts for the ease with which we must suppose a considerable quantity of the pyrogenic substance was continuously absorbed from the bloody contents of the cyst. The results of Angerer's experiments, already mentioned, enable us to explain the source of the fever in this case.

Another instance may be cited in which fever is probably to be explained by the accumulation within the body of products of normal metabolism. More or less fever appears to be a constant accompaniment of the agonizing method of treatment known as the Schroth cure. In this treatment the patient is kept for a number of successive days on dry food with scarcely any fluids. Both Bartels and Jürgensen,[2] who have investigated the nutritive changes of individuals under this treatment, believe that the body becomes so poor in water that some of the products of regressive metamorphosis cannot be carried out of the system. This certainly seems very probable, and, if true, it affords in the light of recent experiments an explanation of the accompanying fever.

I believe that good reasons can be adduced in support of the opinion that the febrile conditions sometimes asso-

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[1] Cramer: Verhandl. d. Deutschen Gesellschaft f. Chirurgie, 13th Congress, 1884.

[2] Jürgensen: Deutsches Arch. f. klin. Med., Bd. i.

ciated with leucocythæmia, profound anæmias, and chlorosis belong to the group of fevers we are now considering. It is probable that some of the obscure ephemeral fevers are also to be included here. But to consider these febrile disorders in detail would lead us into the domain of special etiology upon which we have already perhaps encroached too far. My purpose has been to bring before your attention only a few clinical examples in illustration of the experimental results.

I think that you will agree with me in the conclusion that experimental and clinical evidence justify us in recognizing as a distinct group of pyrogenic agents, substances which have no necessary connection with microorganisms, and which are either not foreign to the healthy organism or are readily formed by unorganized ferments from normal or abnormal constituents of the body. These substances may be described as homologous in distinction from the heterologous agents concerned in the production of septic and infectious fevers.

A class of pyrogenic agents of far greater clinical importance than those previously considered is formed by the products of microörganisms which in themselves are not pathogenic. A considerable number of bacteria, which when inoculated in pure culture into the body are not capable of further invasion or of multiplication, produce in culture fluids and in dead animal or vegetable material poisonous substances often of great virulence. Exception may be taken to the description of these organisms as non-pathogenic, inasmuch as the products of their activity are poisonous, but the epithet pathogenic is usually assigned by bacteriologists only to such microorganisms as are capable of multiplication within the body. If we called all of the microörganisms pathogenic which produce poisonous ptomaines we should have to include in this category a far larger number of the known species of bacteria than has hitherto been customary.

The best known and most important of the fevers produced by chemical products of saprophytic bacteria are those grouped under the name putrid intoxication. Until the introduction of the modern era in bacteriology by Koch nearly all of the experimental work on the etiology of fevers related to the causation of the septic and putrid fevers. It is instructive with our present knowledge to follow the experiments on this subject from the period of Gaspard, Magendie, and Sedillot up to recent times. What light has been shed upon the mass of contradictory and perplexing results of experiments with putrid fluids by the recent chemical and biological studies of putrefactive processes? Some of the putrid substances experimented with undoubtedly contained parasitic microorganisms, and others contained only obligatory saprophytes. Some were rich in poisonous ptomaines, and others were nearly devoid of them. The whole doctrine of the parasitic nature of infectious fevers seems to have hinged in the minds of some upon the determination of the question whether septic and putrid fevers are produced by the absorption of chemical substances, or by the invasion of pathogenic bacteria. The ideas concerning putrid intoxication dominated at one time the whole field of fever etiology, and were applied not only to septicæmia but to typhoid fever, typhus fever, yellow fever—in fact, to nearly all infectious fevers. Nor have the echoes of this period even now entirely died out.

Panum was the first to isolate from putrid materials some chemical substance or substances in tolerable purity, certainly free from bacteria. This substance, when injected into animals, produced symptoms of putrid intoxication. Subsequently, von Bergmann and Schmiedeberg isolated from putrefying yeast a poisonous crystalline substance, their celebrated sepsin. For a time the opinion prevailed that this sepsin is the source of all putrid intoxications. Thanks to the investigations of Nencki and others, and particularly of Brieger, we now

know that many alkaloidal substances can be separated from putrefying materials. Some of these so-called cadaveric alkaloids or ptomaines are poisonous, fever-producing, others are harmless. There is no reason to suppose that the list of the ptomaines of putrefaction has been exhausted, nor is it necessary to believe that all of the poisonous constituents of putrefying materials are of an alkaloidal nature.

Most of the bacteria concerned in ordinary putrefactive processes are purely saprophytic. They are incapable of multiplication in the living animal tissues. In a mixture of putrefactive bacteria it is not, however, uncommon to find genuine pathogenic or parasitic bacteria. It was from such sources that the bacilli of mouse septicæmia and of rabbit septicæmia (Koch) were obtained. The bacillus of malignant œdema is also often found in the early stages of post-mortem decomposition.

There is, of course, no doubt that the absorption of the chemical products of putrefaction may produce fever with septic symptoms, quite independently of the penetration and multiplication within living tissues of bacteria.

Here belong certain cases usually described as septic, in which fever and other bad symptoms subside upon the thorough cleansing and disinfection of a foul wound, or of a puerperal uterus. The majority of cases of septicæmia are not to be included here, for they depend upon the invasion of pathogenic bacteria. But, excluding the cases of genuine septicæmia, there remain the putrid intoxications which result from the absorption of poisonous substances produced in necrotic or disintegrating tissues, or exudations, or extravasated blood, by the action of purely saprophytic bacteria. The ideas which I have expressed on this subject are now so generally admitted that they require no further elucidation.

It is probable that fever, with symptoms of intoxication, although generally of a much milder nature than in the class of cases just considered, may be produced by

abnormal fermentations and putrefactions caused by saprophytic bacteria in the alimentary canal. But here the essential morbid conditions seem to be abnormalities in the gastric and intestinal contents, due partly to the character of the ingesta, but chiefly to alterations of the digestive juices. Fermentative and putrefactive bacteria are normally present in the intestinal canal, and have abundant opportunities to gain access to this situation. The number, however, which can multiply and thrive there is quite limited, for under normal conditions, according to Escherich, only such bacteria can multiply to any extent in the intestinal canal as are capable of growing with little or no oxygen, and of deriving their nourishment from the anaërobic fermentation of the food supplied to them in this situation. Suitable conditions for the excessive multiplication of putrefactive or fermentative bacteria may, however, be furnished by abnormalities of the gastric or intestinal contents.

Of a far more serious nature are the putrid or ptomaine intoxications which result from the ingestion of substances which have undergone outside of the body putrefaction, or changes which lead to the formation of poisonous ptomaines. To this group of cases belong at least many of the instances of poisoning which have been caused by eating certain kinds of meat, sausage, fish, cheese, etc. In some of these instances poisonous ptomaines have been isolated from the suspected substances, but we know scarcely anything of the microörganisms which are concerned in their production.

It is important to bear in mind that it is not stinking putrefaction alone which gives rise to poisonous products. Brieger has found that such products may be absent in very advanced decomposition, and that in general the most virulent products are formed in the early stages of putrefaction. We know, furthermore, that putrefactions and fermentations differ in the character of their products. There are differences according to the kind of bacteria

present, according to the substances decomposed, and according to various other conditions, such as the presence of oxygen, the temperature, etc. This is not the proper occasion to discuss these details.

Enough has been said to prove that we are justified in recognizing as a second class of pyrogenic agents substances which are the products of bacteria in themselves not pathogenic. These pyrogenic agents may be formed on or within the body, or they may be produced outside of the body. I would not by any means have you infer that it has been proven in all of the special examples which I have mentioned, that the bacteria involved are not pathogenic, or capable of multiplication within the living tissues. We have not sufficient knowledge to assert or to deny this in every instance, but I do not think that it is likely exception will be taken to the classification which I have adopted for most of these cases. As has repeatedly been mentioned, our purpose here is not an analysis of individual cases of fever, but an attempt to classify systematically the various pyrogenic substances.

We come now to the third and most important group of fever-producing agents, the pathogenic microörganisms. So overshadowing is their importance that it has been claimed that they are the sole causes of fever. In contrast with former times it is no longer the symptomatic fevers whose etiology is clearest. We have much more definite ideas as to the mode of production of some of the essential fevers which were once the most obscure, than we have of symptomatic fevers. It does not seem to me worth while to go over the chain of evidence which establishes the doctrine that the infectious fevers are caused by microörganisms. There is probably no one who has thoroughly investigated the subject, and is competent to form an opinion on it, who does not to-day admit that a number of infectious diseases have been

proven to depend upon specific microörganisms, and that it is a logical inference that all infectious diseases are caused by parasitic organisms.

It is not germane to our subject to enter into a morphological or biological description of the different species of pathogenic organisms which are causes of febrile diseases. The only question which concerns us in this consideration of the general etiology of fever is how the microörganisms produce fever. Are they themselves the pyrogenic agents, or do they produce chemical substances which are pyrogenic? A number of other possibilities might be mentioned. These and similar questions have suggested themselves to investigators since the beginning of any knowledge of parasitic microorganisms. Our information is far from sufficient to enable us to answer these questions in a positive manner, and still we are not left wholly to vague surmises in attempting to form some sort of an opinion.

That bacteria can produce mechanical effects by plugging up capillaries and in other ways is certain, but the wide differences presented by the various infectious diseases cannot be reconciled with the idea that pathogenic bacteria act chiefly by mere mechanical interference with the fluid and the solid constituents of the body. Notwithstanding the fact that Stricker and Albert succeeded in producing fever by the injection of starch granules into the blood, probably no one will be inclined to attribute the pyrogenic activity of bacteria in any considerable extent to occlusion of bloodvessels.

In a certain number of infectious diseases, particularly of animals, bacteria are present in such enormous number in the blood and tissues that some are inclined to refer the disastrous effects of the organisms to the withdrawal of oxygen and other nutritive pabulum from the cells of the body. So far as the appropriation of oxygen is concerned, this idea is not supported by the results of most of the examinations of the blood in cases

of anthrax. This explanation was more popular in the early days of bacteriology than it is at present, and at the best its value is limited, for it cannot be applied to a large number of infectious diseases, such as cholera or typhoid fever where the circulating blood is not largely invaded by the parasites. Furthermore, it is not clear how the appropriation by bacteria of nutriment intended for the tissues would help us to explain the production of fever.

It has been suggested that the increased temperature in infectious fevers may be explained by the heat produced by oxidation or other chemical changes in the microörganisms themselves. But this is not at all a satisfactory explanation. Not only is the quantity of heat which can come from this source in all probability very small compared with that constantly produced in the body, but such an explanation of febrile rise of temperature is not in harmony with what we know concerning the mode of production of fever (see Lecture I.).

The failure to explain the pathogenic power of bacteria in these and similar ways led to the supposition that the morbid activity of pathogenic bacteria is exerted chiefly by means of injurious chemical products. The demonstration of such products leaves no room for doubt as to the correctness of this supposition for some infectious diseases. This explanation is probable for most such diseases, but experience has shown that it is particularly dangerous to indulge in hasty generalizations in this department of medical science.

Sterilized and filtered cultures, particularly old cultures, of various pathogenic bacteria are capable of producing fever and other symptoms when injected into the blood or tissues. This, of course, makes it evident that the bacteria in question give rise to poisonous substances. It is necessary to distinguish between the intoxication produced by the injurious products of bacteria and the infection caused by multiplication of the microör-

ganisms within the body. That this distinction may be readily overlooked is shown by the recent experiments with the inoculation into animals of pure cultures of the typhoid bacillus. Small quantities of these cultures may be inoculated without any apparent effect; if, however, larger quantities are injected into the veins or the peritoneal cavity of a rabbit, the animal dies in a short time and the characteristic bacilli are found in the blood, spleen, and elsewhere. It was supposed by Fränkel and Simmonds,[1] to whom we owe this latter observation, that actual infection took place, but it has been demonstrated by Sirotinin and by Beumer and Peiper[2] that under these circumstances no multiplication of the injected bacilli occurs, and that the same results may be obtained by the injection of sterilized typhoid cultures.

The isolation in a chemically pure state of the poisonous products of pathogenic bacteria encounters great difficulties, and we owe to Brieger[3] nearly all that has been accomplished in this direction. Two substances which he has obtained from cultures of pathogenic bacteria are of great interest. Brieger isolated from pure cultures of the typhoid bacillus a very poisonous ptomaine or toxine, as he prefers to call this group of substances. He has given to it the name typhotoxine. It may be somewhat significant that he failed to find typhotoxine in a culture which had stood for twenty-four hours at a temperature of 102.2° F. (39° C.). The injection of typhotoxine into guinea-pigs produced great muscular weakness, diarrhœa, increased frequency of pulse and of respiration, and death. Nothing is said as to the effect upon the temperature of the animal.

A toxine has been isolated by Brieger in a crystalline

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[1] Fränkel and Simmonds: Die Ætiologische Bedeutung des Typhus-bacillus, Hamburg und Leipzig, 1886.

[2] Sirotinin: Zeitschrift f. Hygiene, Bd. i. 465.
Beumer u. Peiper: Ibid., p. 489.

[3] Brieger: Untersuchungen über Ptomaine, Berlin, 1886.

form from an impure culture of the tetanus bacillus. This substance, called tetanin, produces, when injected into animals, the characteristic symptoms of tetanus.

It is evident that these important discoveries render far more definite than was formerly possible, the belief that bacteria produce fever by means of their chemical products.

A dangerous influence exerted by poisonous ptomaines is that under their agency the power of the body of resisting the invasion of various microörganisms may be impaired or overcome. Thus, Wyssokowitsch has shown that the immunity of some animals against certain species of bacteria may be destroyed by ptomaine poisoning.

In order to observe the effects upon the temperature, I have injected into rabbits sterilized cultures of the typhoid bacillus. Injections of very small quantities of these cultures produce no effects, somewhat larger amounts cause a rise of temperature without other marked symptoms, still larger quantities produce increased temperature, diarrhœa, weakness, and other manifest symptoms of severe illness, but the animal may recover; relatively large amounts are followed by fall of temperature, grave illness, and death. I have also obtained results similar to those of Sirotinin, who inoculated two rabbits with the same amount of a typhoid culture. In one rabbit fever developed and the animal recovered; in the other, the temperature fell after the injection, and the animal died. This certainly does not indicate that the rise of temperature in itself is an unwelcome attendant of intoxication with the poisonous products of bacteria. My experiments certainly showed that the animals were more likely to die after injection of typhoid cultures when the temperature fell than when it rose, independently of the quantity of material injected. One is reminded here of the very malignant cases of typhoid fever reported by Fräntzel, and others, in which the temperature throughout

a great part of the disease was subfebrile, or even at times subnormal.

In no disease is the dependence of the febrile paroxysm upon the presence of bacteria so apparent as in relapsing fever, where, according to the statements of most, although not of all, observers the spirilla appear in the blood at the beginning of a paroxysm and disappear at the end. Whether or not, here and in malaria, the pyrogenic agent is a chemical product of the microörganisms causing the disease, we do not know.

I must content myself with having brought before you evidence showing that at least in some of the infectious fevers the specific bacteria produce pyrogenic substances. We have no right to say that this is the only way in which pathogenic bacteria can cause fever.

We have considered now three groups of agents concerned in the production of fever, viz.: first, unorganized ferments and other relatively homologous substances; second, ptomaines and other chemical products of saprophytic microörganisms; third, pathogenic microörganisms and their chemical products.

It is not to be understood that these groups correspond to sharply defined classes of fever-producing agents. The same substance may be produced by the action of unorganized ferments, as well as by saprophytic bacteria or by parasitic bacteria; hence, we may find the same fever-producing agent in each of the three groups. As has already been mentioned, our knowledge does not justify us in regarding these various substances as the immediate and direct pyrogenic agents. The epithet pyrogenic is applied to them only by a certain latitude of signification. It is possible that these various substances, which we are in the habit of describing as pyrogenic, may produce in the body some common change which gives rise to the real fever-producing agent. This is the view of von Bergmann and Angerer, who believe that this common change is a liberation of fibrin ferment by

destruction of leucocytes. While we cannot consider this view as more than an hypothesis, it is, nevertheless, well to remember that apparently heterogeneous substances, which are usually designated as pyrogenic, may produce similar changes which are to be regarded as the real source of the febrile disorder of animal heat. But, notwithstanding these limitations and these elements of uncertainty, it seems to me that some such classification as that suggested of the agents producing fever is more useful than that usually employed in the discussions of the etiology of symptomatic and of essential fevers.

There is one point which must be impressed upon every one who makes many experiments with pyrexial agents. This is, that once in a while a substance of undoubted pyrogenic power causes a fall instead of a rise of temperature. This occurs frequently when the substance is injected in large quantity and under these circumstances there is usually produced a condition of collapse. But in exceptional cases the same dose which will cause in one animal a rise of temperature may give rise in another animal of the same species to a distinct reduction of temperature. In these latter cases there must be some idiosyncrasy on the part of the animal. Aronsohn[1] refers this unusual phenomenon to some peculiarity of the heat centres in the brain, and he draws an interesting parallel between this contrary effect of pyrogenic substances and the exceptional cases in which antipyretic drugs give rise to elevation instead of lowering of temperature.

The causes of fever which we have thus far discussed, have been substances which exert a pyrogenic effect when introduced into the circulation. We suppose that these substances act in some way upon the nervous system, but whether or not this action is a primary one it is impossible to say. Even if we assume, as is often done,

[1] Aronsohn: Deutsche med. Wochenschrift, 1888.

that these substances incite directly in the blood and tissues chemical changes which lead to increased production of heat, we must still have recourse to some action upon the nervous system, as has already been sufficiently set forth in the previous lectures.

It cannot be doubted that fever may be caused by other agencies than pyrogenic substances present in the blood or tissues. The effects of exposure to external heat have already been considered. We found experimental evidence in support of the view ably advocated by H. C. Wood, that in typical cases of thermic fever or sunstroke, the strain placed upon the heat-regulating centres by exposure to excessive heat results in paralysis of these centres with rapid elevation of the internal temperature.

The cause of the elevation of temperature in tetanus is not altogether clear. In this disease the temperature may vary but little from the normal, but it is not uncommon to find excessive elevations of temperature toward the termination. Temperatures of 113° F. (45° C.), or more, have been recorded. The idea would naturally suggest itself that the rise of temperature is due to the tetanic muscular spasms, which we know to be accompanied by production of heat. Leyden was led to adopt this explanation by the results of experiments made upon animals. He succeeded by producing violent tetanic contractions of the muscles of a dog, in raising the internal temperature in the course of one hour and a half from 103.3° F. (39.6° C.) to 112.6° F. (44.8° C.). Clinical observations, however, do not support the supposition that the hyperpyretic temperatures of tetanus are dependent upon the muscular contractions. In spite of violent and prolonged tetanic spasms, the internal temperature may remain normal or be but slightly elevated. There is a decided similarity between the hyperpyrexia of tetanus and that which occurs in rheumatism and some other diseases, particularly in affections of the central

nervous system, and it certainly seems probable that in all of these cases there is a profound disturbance of the heat-regulating centres. As the elimination of urea in tetanus is not excessive, we find additional reason to separate tetanic hyperpyrexia from ordinary febrile conditions. Recent investigations of the etiology of tetanus, have rendered it certain that at least some forms of this disease are caused by infection with a special micro-organism. This has been demonstrated not only in the tetanus of animals but also in that of human beings. The tetanus bacillus has been found wide-spread in the ground in Germany, and I find it abundant in the ground in Baltimore and its neighborhood. In experimental tetanus, the bacillus, which has not yet been obtained in perfectly pure cultures, develops chiefly in the tissues near the seat of inoculation, and does not invade other parts of the body and the blood to any great extent. This indicates that the symptoms are referable chiefly to poisoning by some chemical products of the specific microörganism. As has already been mentioned, this view is sustained by Brieger's discovery in cultures containing the tetanus bacillus of a peculiar ptomaine which he has called tetanin, and which produces tonic spasms of the muscles. It is, therefore, reasonable to believe that the hyperpyrexia of tetanus is caused by the action of poisonous products of the tetanus bacillus on the nervous centres concerned in temperature regulation. Our present knowledge, however, does not warrant us in asserting that all forms of tetanus in human beings are of an infectious nature.

In the first lecture of this course, evidence was presented to show that pyrexia may be caused by affections of the nervous system without the agency of any pyrogenic substance. It may jar upon the sensibilities of some to call this form of pyrexia fever; but this hesitation can be due only to the idea that symptoms which are referable to infection or intoxication are essential to

the conception of fever. In my judgment, we shall be led into confusion if we attempt to incorporate into our definition of fever, more than properly belongs to the febrile disorder of animal heat, and from this point of view there can be no impropriety in designating as fever, the pyrexia dependent directly upon affections of the nervous system.

It is not necessary to repeat here the conclusive experimental evidence for the existence in the nervous system of centres or regions which control the dissipation of heat and the chemical processes concerned in the production of heat. Those who are not much impressed by experiments upon animals, can hardly fail to be convinced by the clinical evidence which demonstrates that lesions of the nervous system may cause elevation of temperature, which cannot be referred to the action of any pyrogenic substance. Such evidence must, of course, be collected from cases where the fever cannot be explained by inflammation, bed-sores, or other lesions which can give rise to absorption fever. W. Hale White,[1] in the interesting article already referred to, has collected a number of cases of tumor, hemorrhage, softening, sclerosis, injury and functional disturbance of the spinal cord and brain, in which the pyrexia or hyperpyrexia is to be explained only by the lesion of the nervous system. The number of such cases might be considerably increased. These cases show that lesions of the cervical part of the cord, of the pons, of the corpus striatum, and of the neighboring white matter, are most likely to be associated with high temperature, but the cases hitherto reported hardly justify positive statements as to the exact situation in man of thermically active nerves or regions in the brain and spinal cord. As might be expected, not only focal lesions, but also diffuse diseases such as occur

[1] W. Hale White: The Theory of a Heat Centre from a Clinical Point of View. Guy's Hospital Reports, vol. 42, 1884.

in general paralysis of the insane, locomotor ataxia, multiple sclerosis may give rise to pyrexia which sometimes assumes the form of temperature crises. It is in harmony with what we know of other disorders of the nervous system, to find that not only demonstrable anatomical lesions, but also functional disturbances may produce nervous pyrexia. Such functional disturbance furnishes the most probable explanation of the singular and erratic elevations of temperature which have been occasionally observed in hysteria.

A question which merits more consideration than it is possible to give to it on the present occasion, relates to the possibility of the occurrence of fever as a reflex neurosis. The advance in our knowledge of the etiology of traumatic and inflammatory fevers, has pushed aside almost wholly the old doctrine of irritative fever. There are, however, cases of fever where still the simplest, and apparently most rational, explanation of the causation, is peripheral nerve irritation. As examples may be mentioned, the fever resulting from teething in children, that sometimes accompanying the passage of gall-stones or urinary calculi, and that occasionally following the insertion of a catheter into the urethra. It must be admitted that the evidence on this point is not conclusive. Especially is there lack of satisfactory experimental evidence. Electrical irritation of the exposed sciatic nerve is, under ordinary circumstances, followed by a moderate fall of temperature, although Ott[1] finds that in atropinized cats such irritation is followed by a decided rise of temperature. But these experiments cannot be held to weigh for or against the doctrine of irritative fever. Observations on human beings indicate that peripheral nerve irritation, if ever a cause of fever, is so only in certain situations and under certain forms of stimulation, and in certain individuals. In infants temperature regulation is

[1] Ott: Therapeutic Gazette, August, 1887.

more labile than in adults, so that it may be that nerve irritation can more readily disturb the temperature in the former than in the latter. The chief controversy as to the question now before us, has been as to the explanation of certain forms of urethral or catheter fever. It cannot be doubted that a large number, probably most, of the cases of so-called urethral fever, are instances of genuine absorption fever. Even if we exclude all cases with diseased kidneys, or with cystitis or other inflammatory disease of the urinary passages, there remains a certain number of cases in which the gentle insertion of a disinfected catheter is followed by distinct febrile reaction. It seems unwarrantable to assume that in all of these cases the catheter has caused a laceration of the urethra through which pyrogenic substances are absorbed. What is the nature and whence the source of these substances? In the cases now under consideration, they can be sought only in the normal urine, and of their existence there no proof has been afforded. In these cases it is certainly very difficult to understand how the fever can be interpreted as due to the absorption of some pyrogenic agent, and failing this explanation, the idea that the fever is dependent upon nerve irritation is most plausible.

I have now presented to you an imperfect survey of the general etiology of fever. The attempt has been made to classify the leading causes of fever, but it cannot be claimed that every variety of fever can be assigned to one of these groups of causes. Our knowledge of the etiology of special fevers is still too imperfect to warrant any such generalization. This is an attractive field for much patient investigation. I need only remind you of the uncertainty which still pertains to the causation of many of the fevers of warm countries. There is reason to believe that there remain yet to be differentiated etiologically, specific types of fever which occur among us, and particularly in our Southern States. It may be,

that increasing knowledge will necessitate the recognition of varieties of pyrogenic agents entirely distinct from any with which we are now familiar. It is certain that future investigations will add clearness and precision to our ideas of the nature and mode of action of causes of fever which, at the best, we can now understand only imperfectly.

I cannot conclude this course of lectures without saying a few words on a subject which must engage the attention of every one who gives much thought to the nature of fever. What is the significance of fever, is a question which thrusts itself upon us no less than it has upon physicians in all ages. Unfortunately, we cannot to-day, any more than could our predecessors, give other than a speculative answer to this question. There have been in all ages enlightened physicians who have held the opinion that fever is a process which aids in the elimination or destruction of injurious substances which gain access to the body. Under the influence of ideas which sought in increased temperature the origin of the grave symptoms of fever, we have in recent times in great part lost sight of the doctrine once prevalent, that there may be in fever a conservative element. There is much which speaks in favor of this doctrine. The real enemy in most fevers, is the noxious substance which invades the body, and there is nothing to prevent us from believing that fever is a weapon employed by nature to combat the assaults of this enemy. The doctrine of evolution indicates that a process which characterizes the reaction of all warm-blooded animals against the invasion of a host of harmful substances, has not been developed to so wide an extent, and is not retained with such pertinacity without subserving some useful purpose. This is a point of view from which many pathological processes can be regarded with advantage. Even suppuration, which one does not generally look upon as a beneficent provision, is a most important instrument of nature in forming a

barrier against general infection of the body with certain microörganisms. It is impossible with our present knowledge, to say in exactly what way fever accomplishes a useful purpose. There are facts which suggest that in some cases of fever the increased temperature as such may impair the vitality or check the virulence of pathogenic microörganisms, but there are many circumstances which make it difficult to suppose that this is the agency by which fever usually exerts a favorable action.

The supposition seems to me more probable that the increased oxidation of fever aids in the destruction of injurious substances. According to this view, the fever-producing agents light the fire which consumes them. It is not incompatible with this conception of fever, to suppose that the fire may prove injurious also to the patient and may require the controlling hand of the physician. Time will not permit me to elaborate further the ideas here suggested. In the course of these lectures some facts have been presented and others might be drawn from clinical and experimental observations which favor the hypothesis that fever is in a certain sense a conservative process. Unproven and intangible as the hypothesis may seem to some, no apology is needed for bringing to your attention a conception of fever in favor of which much can be adduced, and which, if true, is of fundamental importance, both theoretically and practically.

The Cartwright Lectures.

ON THE

GENERAL PATHOLOGY OF FEVER.

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